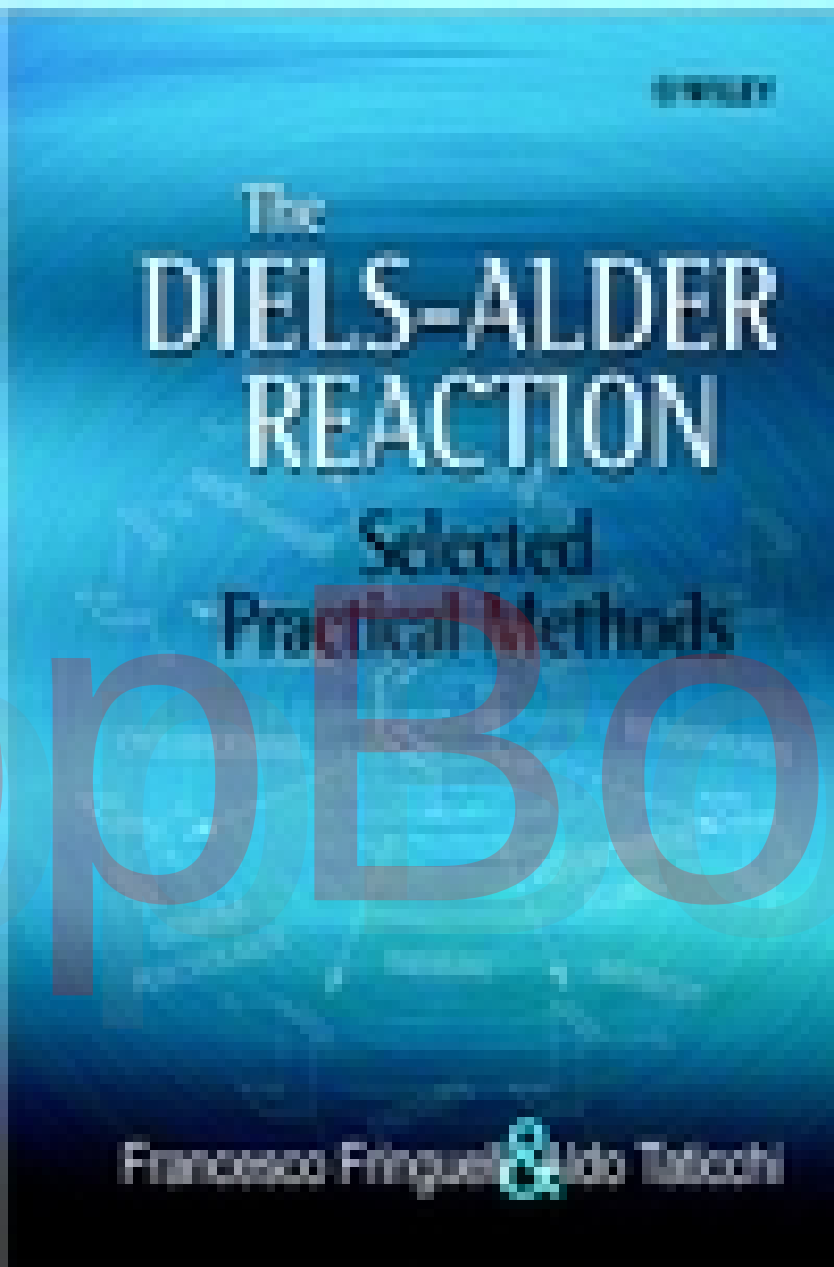
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REACTION
Selected
Practical Methods
Francesco Fringuelli & Aldo Taticchi

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Preface

The Diels-Alder reaction, probably the most widely used methodology in organic synthesis today, has contributed greatly to the development of mechanistic and theoretical chemistry. The recent discovery of a Diels–Alderase enzyme has provided insights into the mechanism of biosynthetic cycloaddition.

As a follow-up to our book *Dienes in the Diels–Alder Reaction* (1990) and in light of our personal experience as well as the reviews and books that have been published on this topic to date, we decided that a book collecting and describing the experimental methods that have been developed to perform the Diels–Alder reaction would be a useful tool for researchers working in organic synthesis.

The first chapter presents the general aspects of the reaction; Chapters 2–6 illustrate the various methods and their applications in organic synthesis. At the end of each chapter a list of graphically abstracted Diels–Alder reactions is presented to show selected synthetic applications of the specific methodology. The discussion of the various topics is not exhaustive because our aim has been to emphasize the synthetic potential of each method. Chapter 7 reports a list of books, reviews, monographs and symposia proceedings which have appeared since 1990 and an index of keywords to help the reader find a particular paper of interest.

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The book is directed toward undergraduate and graduate level students, as well as to academic and industrial researchers working in organic synthesis.

We are grateful to Drs Assunta Marrocchi, Oriana Piermatti and Luigi Vaccaro for their assistance with the drawings.

Francesco Fringuelli
Aldo Taticchi

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Abbreviations and Acronyms

Ac	acetyl
acac	acetylacetonate
AIBN	2,2′-azobisisobutyronitrile
Ar	aryl
9-BBN	9-borabicyclo-[3.3.1]-nonyl
BINOL	1,1′-bi-2-naphthol
BLA	Brønsted Lewis acid
BMIM	1-butyl-3-methylimidazolium cation
Bn	benzyl
BOM	benzyloxymethyl
BP	N-1-butylpyridinium cation
Bu	*n*-butyl
i-Bu	*iso*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl
CAB	chiral acyloxyborane
CAN	ceric ammonium nitrate
Cat	catalyst
Cat*	chiral catalyst
CBZ or Cbz	benzyloxycarbonyl or carbobenzyloxy
COD	cyclooctadiene
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
CTAB	cetyltrimethylammonium bromide
Cy	cyclohexyl
DBU	1,8-diazabicyclo-[5.4.0]-undec-7-ene
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzo-quinone
de	diastereoisomeric excess
DIEA	diisopropylethylamine
DIPHOS	bis-(1,2-diphenylphosphino)-ethane
DMAD	dimethyl acetylenedicarboxylate
DMF	dimethyl formamide
DMI	1,2-dimethylimidazole
DPP	2,6-diphenylpyridine

dppe	2-(diphenylphosphino)ethyl
dppp	1,3-bis(diphenylphosphino) propane
DS	dodecyl sulfate
DTBMP	2,6-di-*t*-butyl-4-methylpyridine
DTBP	2,6-di-*t*-butylpyridine
E	CO_2Me if not otherwise specified
EDDA	ethylene diammonium diacetate
ee	enantiomeric excess
EG	ethylene glycol
EGA	electrogenerated acid
EMIM	1-ethyl-3-methylimidazolium cation
FMO	frontier molecular orbital
Fu	furyl
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HP	high pressure
HSVM	high-speed vibration milling
HTBA	hexadecyltrimethylammonium bromide
IP	incident power
IPB	isopropylbenzene
LASC	Lewis-acid surfactant combined catalyst
LDA	lithium diisopropylamide
Ln	lanthanides
LP-DE	lithium perchlorate-diethyl ether
LP-NM	lithium perchlorate-nitromethane
LT-AC	lithiumtrifluoromethanesulfonamide-acetone
LT-DE	lithiumtrifluoromethanesulfonamide-diethylether
LUMO	lowest occupied molecular orbital
MABR	methylaluminum-bis-(4-bromo-2,6-di-*tert*-butylphenoxide)
MAD	methylaluminum-bis-(4-methyl-2,6-di-*tert*- butylphenoxide)
Men	menthyl
MeOSMT	methoxytrimethylsilane
MO	molecular orbital
MOM	methoxymethyl
MPM or PMB	*p*-methoxybenzyl or *p*-methoxyphenyl-methyl
MS	molecular sieves
MW	microwave
NBS	N-bromosuccinimide

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NMI	1-methylimidazole
NPM	N-phenylmaleimide
PCP	*p*-chlorophenol
Ph	phenyl
PMB or MPM	*p*-methoxybenzyl or *p*-methoxyphenyl-methyl
Pr	*n*-propyl
i-Pr	*iso*-propyl
PS-DES	polystyrene diethylsilane
Py	pyridil
Rfx	reflux
rt	room temperature
SBT or TBS or SMDBT or TBDMS	*t*-butyldimethylsilyl
SCF	supercritical fluid
SDS	sodium dodecyl sulfate
SMDBT or TBDMS or SBT or TBS	*t*-butyldimethylsilyl
SMT or TMS	trimethylsilyl
SPDBT or TBDPS	*t*-butyldiphenylsilyl
SPT or TPS	triphenylsilyl
TADDOL	$\alpha, \alpha, \alpha', \alpha'$-tetraaryl-1,3-dioxolane-2-dimethyl-4,5-dimethanol
TBAF	tetra-*n*-butylammonium fluoride
TBDMS or SMDBT or TBS or SBT	*t*-butyldimethylsilyl
TBDPS or SPDBT	*t*-butyldiphenylsilyl
TBME	*t*-butyl methyl ether
TBPA	tris(bromophenyl)ammoniumhexa-chloroantimoniate
TBS or SBT or TBDMS or SMDBT	*t*-butyldimethylsilyl
TCNE	tetracyanoethylene
TES	triethylsilyl
Tf	trifluoromethanesulfonyl (trifyl)
TFA	trifluoroacetic acid
TFE	1,1,1-trifluoroethanol
TFMSA or TfOH	trifluoromethanesulfonic acid
TfOH or TFMSA	trifluoromethanesulfonic acid
Th	thienyl
THF	tetrahydrofuran
Thx	2,3-dimethyl-2-butyl (thexyl)
TMOF	trimethyl orthoformate
TMS or SMT	trimethylsilyl
TMSOTf	trimethylsilyl trifluoromethane sulfonate
Tol	tolyl
TPS or SPT	triphenylsilyl

Ts	tosyl or *p*-toluensulfonyl
TTA	tris-(*p*-tolyl)aminium
TTMSS	tris-trimethylsilylsilane
US	ultrasonic, ultrasonication
Δ	heating

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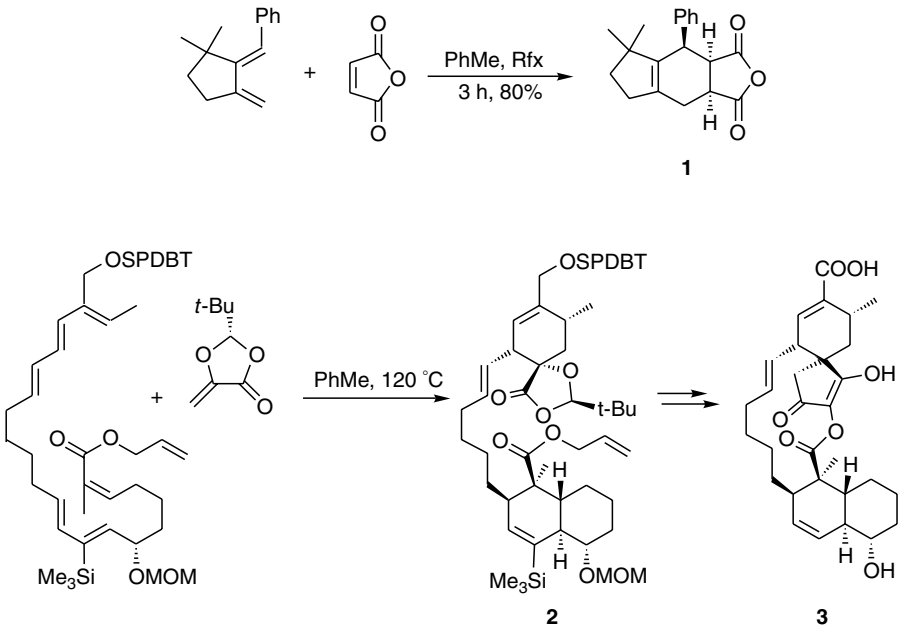
1 Diels–Alder Reaction: General Remarks

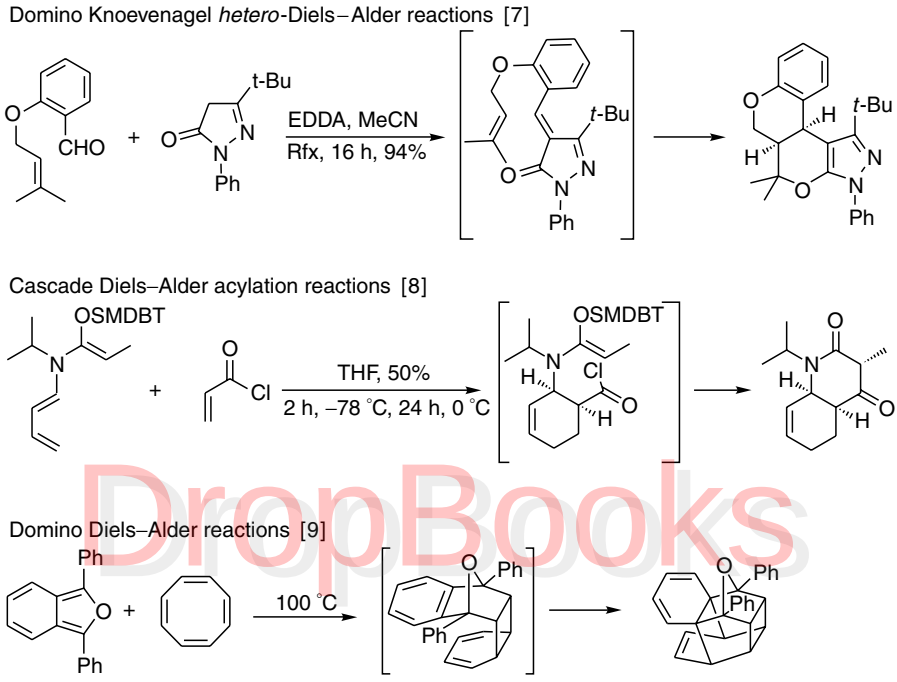
1.1 INTRODUCTION

The Diels–Alder cycloaddition is the best-known organic reaction that is widely used to construct, in a regio- and stereo-controlled way, a six-membered ring with up to four stereogenic centers. With the potential of forming carbon–carbon, carbon–heteroatom and heteroatom–heteroatom bonds, the reaction is a versatile synthetic tool for constructing simple and complex molecules [1]. Scheme 1.1 illustrates two examples: the synthesis of a small molecule such as the tricyclic compound **1** by intermolecular Diels–Alder reaction [2] and the construction of a complex compound, like **2**, which is the key intermediate in the synthesis of (−)chlorothricolide **3**, by a combination of an intermolecular and an intramolecular Diels–Alder cycloaddition [3].



Scheme 1.1

To rapidly construct complex structures, a recent synthetic strategy uses the Diels–Alder cycloaddition in sequence with another Diels–Alder reaction or with other reactions without isolating the intermediates (domino, tandem, cascade, consecutive, etc., reactions) [4–6]. Scheme 1.2 illustrates some examples.



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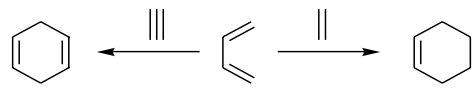
Scheme 1.2

The main purpose of this chapter is to introduce the various aspects of the Diels–Alder cycloaddition and the terminology employed.

Since its discovery in 1928 [10], more than 17 000 papers have been published concerning synthetic, mechanistic and theoretical aspects of the reaction and about half of these have appeared in the last decade.

The classical Diels–Alder reaction is a cycloaddition between a conjugated diene and a second component, called dienophile, which has at least a π bond (Equation 1.1). When one or more heteroatoms are present in the diene and/or dienophile framework, the cycloaddition is called a *hetero-Diels–Alder* reaction.



(1.1)

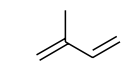
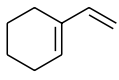
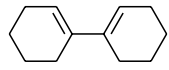
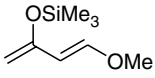
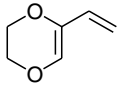
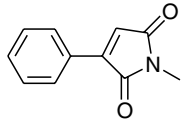
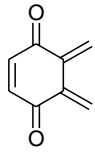
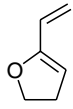
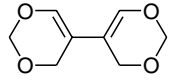
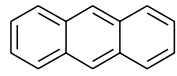
The reaction is classified as a $[_{\pi}4_s +_{\pi}2_s]$ cycloaddition; 4 and 2 identify both the number of π electrons involved in the electronic rearrangement and the number of atoms originating the unsaturated six-membered ring. The subscript *s* indicates that the reaction takes place suprafacially on both components. There are other $[_{\pi}4_s +_{\pi}2_s]$ reactions, and therefore it is the term *Diels–Alder* which specifies this particular type of reaction.

The Diels–Alder reaction can be *intermolecular* or *intramolecular* and can be carried out under a variety of experimental conditions that will be illustrated in detail in the following chapters.

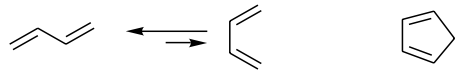
1.2 DIENE AND DIENOPHILE

A great variety of conjugated dienes have been used and many of them have been collected and classified [1a]. Table 1.1 illustrates some examples. Conjugated dienes react providing that the two double bonds have or can assume a *cisoid* geometry (Equation 1.2). A *transoid* diene (Equation 1.3) would give an energetically very unfavorable six-membered ring having a *trans* double bond. Cyclic dienes are generally more reactive than the open chain ones. The electronic effects of the substituents in the diene influence the rate of cycloaddition [11]. Electron-donating substituted dienes accelerate the reaction with electron-withdrawing substituted dienophiles (*normal electron-demand Diels–Alder reaction*) (Equation 1.4) [12], whereas electron-withdrawing groups in the diene accelerate the cycloaddition with dienophiles having electron-donating groups (*inverse electron-demand Diels–Alder reaction*)

Table 1.1 Representative dienes

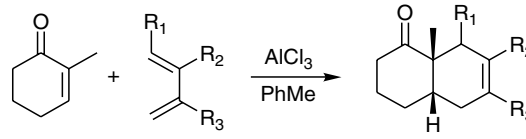
Open chain	Outer ring	Inner-outer ring	Across ring	Inner ring
				
				
				

(Equation 1.5) [13]. Diels–Alder reactions which are insensitive to the substituent effects in the diene and/or dienophile are classified as *neutral* (Equation 1.6) [14].



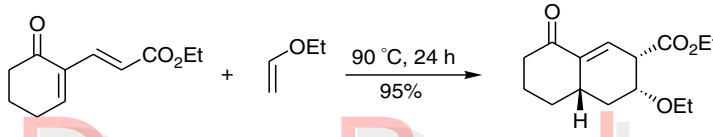
(1.2)

(1.3)



(1.4)

R_1, R_2, R_3 = H, Me



(1.5)

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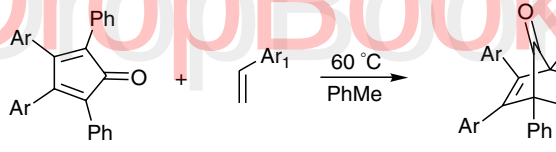


(1.6)

Ar = C_6H_4Y (Y = H, p-OMe, p-NMe_2)

Ar_1 = C_6H_4Y (Y = H, p-OMe, p-NMe_2, p-Cl, p-NO_2, m-NO_2)

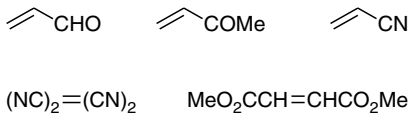
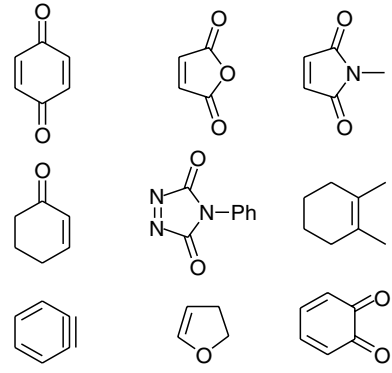
Dienophiles are molecules possessing a double or triple bond. They are more numerous and more variegated than dienes [1]. Typical dienophiles are illustrated in Table 1.2.

The simplest dienophile, ethene, is poorly reactive. Electron-withdrawing and electron-donating groups, on the carbon atom double bond, activate the double bond in normal and inverse electron-demand Diels–Alder reactions, respectively.

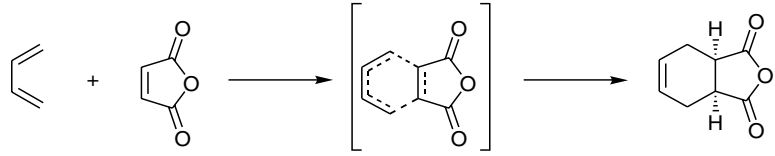
1.3 PERICYCLIC DIELS–ALDER REACTION

The Diels–Alder reaction is a pericyclic cycloaddition when bond-forming and bond-breaking processes are concerted in the six-membered transition state

Table 1.2 Representative dienophiles

Acyclic	Cyclic
	

(Equation 1.7). A concerted synchronous transition state [15] (the formation of new bonds occurs simultaneously) and a concerted asynchronous transition state [16] (the formation of one σ bond proceeds in advance of the other) have been suggested, and the pathway of the reaction depends on the nature of the reagents and the experimental conditions [17].



(1.7)

Most Diels–Alder reactions, particularly the thermal ones and those involving apolar dienes and dienophiles, are described by a concerted mechanism [17]. The reaction between 1,3-butadiene and ethene is a prototype of concerted synchronous reactions that have been investigated both experimentally and theoretically [18]. A concerted unsymmetrical transition state has been invoked to justify the stereochemistry of $AlCl_3$-catalyzed cycloadditions of alkylcyclohexenones with methyl-butadienes [12]. The high *syn* stereospecificity of the reaction, the low solvent effect on the reaction rate, and the large negative values of both activation entropy and activation volume comprise the chemical evidence usually given in favor of a pericyclic Diels–Alder reaction.

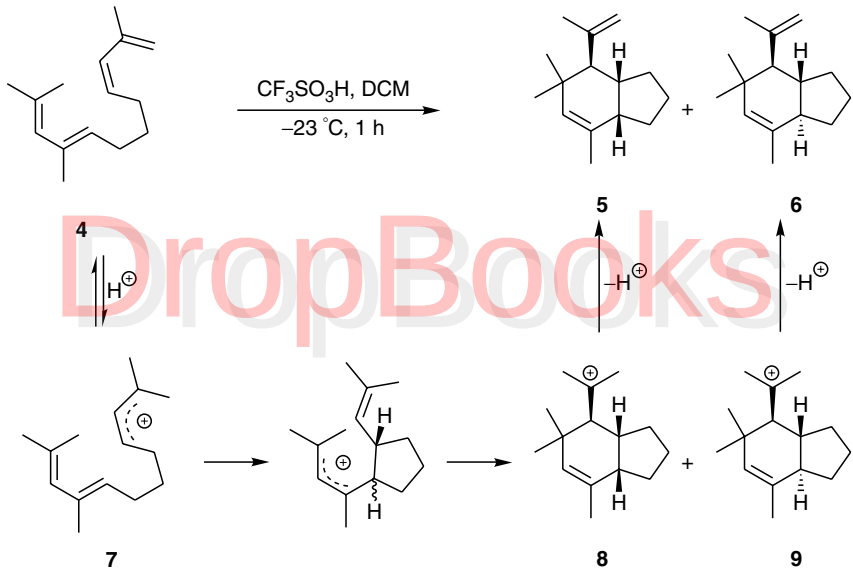
1.4 IONIC AND RADICAL DIELS–ALDER REACTIONS

Conjugated cations, anions and radicals can give the Diels–Alder reaction. In such a case, the two σ bonds are formed in two separate steps (stepwise

mechanism) and the cycloaddition is not pericyclic [19]. Both cationic and cation radical Diels–Alder reactions were recently reviewed [20].

Extensive studies by Gorman and Gassman have shown that an allyl cation can be a 2π-electron component in a normal electron-demand cationic Diels–Alder reaction and, since a carbocation is a very strong electron-withdrawing group, the allyl cation is a highly reactive dienophile [19a, 21].

Tetraene **4** (Scheme 1.3), when treated with 40 mol % of triflic acid in methylene chloride at −23 °C for 1 h, gives the adducts **5** and **6** in a 1:1 ratio as the main reaction products. The formation of these adducts has been justified [21] by a stepwise mechanism that requires an initial reversible protonation of **4** to produce the allyl cation **7**, which then cyclizes to **8** and **9** in a non-reversible process. Deprotonation of **8** and **9** gives **5** and **6**, respectively.



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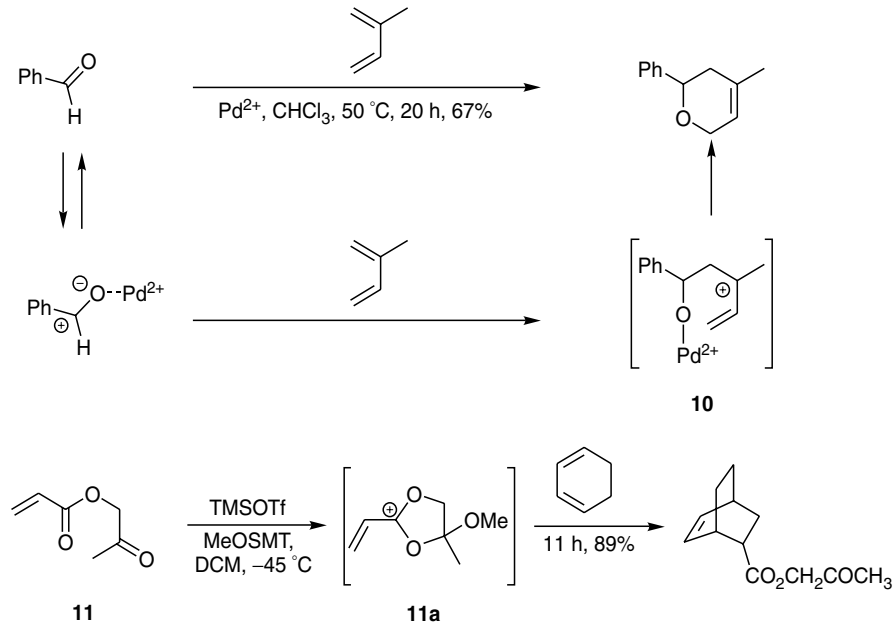
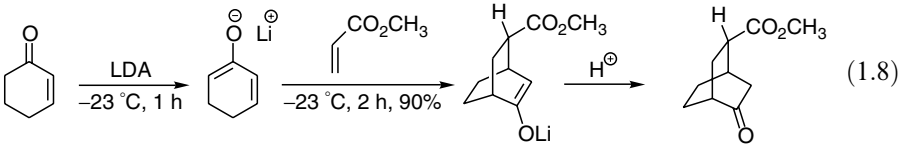
Scheme 1.3

Other examples that involve intermediate allyl cations are illustrated in Scheme 1.4. The cationic palladium(II) complex $[Pd(dppp)(PhCN)_2](BF_4)_2$ coordinates the carbonyl oxygen of benzaldehyde and the activated carbonyl carbon attacks the isoprene, forming the allyl cation **10** which then cyclizes to give the 4-methyl-6-phenyl-5,6-dihydro-2H-pyran [22]. 2-Oxopropyl acrylate **11**, in the presence of trimethylsilyltrifluoromethane sulfonate (TMSOTf) and methoxytrimethylsilane (MeOSMT), generates the cation **11a** which is an efficient dienophile that reacts easily with the cyclohexadiene to give the Diels–Alder adduct in good yield [23].

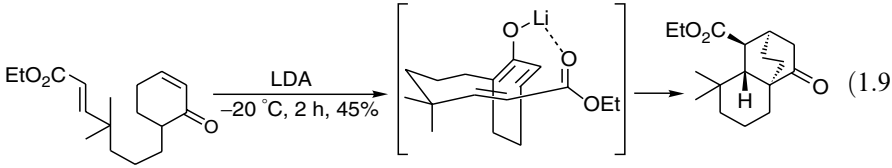


Scheme 1.4

Anionic Diels–Alder reactions have been studied less extensively with the interest having been focused mainly on the cycloaddition of enolates of α,β-unsaturated ketones with electron-poor olefins [24] (Equations 1.8 and 1.9). These reactions are fast and stereoselective and can be regarded as a sequential double Michael condensation, but a mechanism involving a Diels–Alder cycloaddition seems to be preferred [24b,f, 25].



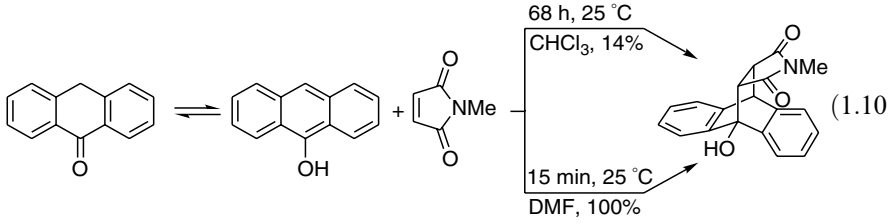
(1.8)



(1.9)

The first evidence of an anionic Diels–Alder reaction was given by Rickborn [25a]. The reaction of anthrone with N-methylmaleimide in $CHCl_3$ or THF occurs with low yield [26] (Equation 1.10), while in DMF or in the presence of catalytic amounts of amine (Et_3N, Py) the reaction is completed in a few minutes [25].

The cycloaddition is ascribable to the oxyanion of hydrogen-bonded enolate ($ArO^{\ominus}$---$HNEt_3^{\oplus}$) rather than to the hydrogen-bonded enol (ArOH---NEt_3). An enantioselective version of the reaction was achieved by using a homochiral amine [27]. Similarly the reactions with less reactive dienophiles such as dimethyl fumarate, fumaronitrile, maleonitrile and methyl acrylate give the Diels–Alder adducts quantitatively when the cycloadditions are carried out in THF or $CHCl_3$ in the presence of Et_3N, while in MeOH Michael adducts were isolated. Experimental evidence supports the hypothesis that the base-catalyzed cycloadditions of anthrone with dienophiles are concerted Diels–Alder processes [25b].



(1.10)

Radical Diels–Alder reactions have been used mainly to synthesize polycyclic molecules. These reactions, like those that involve cations and anions as components, proceed quickly but generally do not give high yields. Thus, the tricyclic enone **14** is the result of an intramolecular Diels–Alder reaction of quenched vinyl radical intermediate **13** obtained by treating the iododienynone **12** with *n*-tributyltin hydride/2,2′-azobisisobutyronitrile (AIBN) [28] (Equation 1.11).

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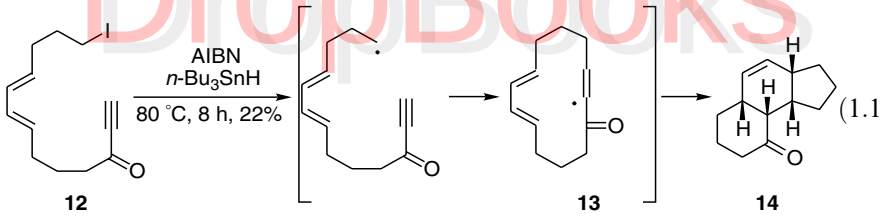
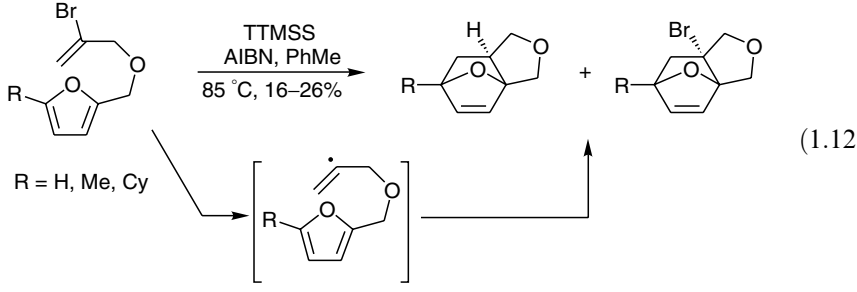


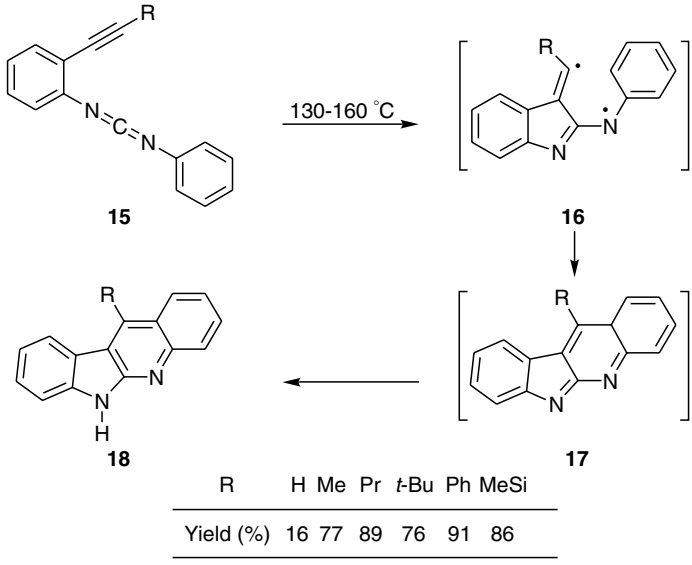
(1.11)

Heteropolycyclic compounds were obtained [29] by treating bromo furylethers with tris-(trimethylsilyl)silane (TTMSS) in hot toluene containing a catalytic amount of AIBN (Equation 1.12).



(1.12)

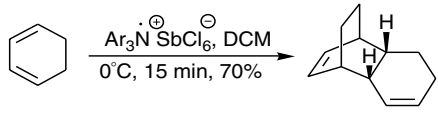
Wang recently reported [30] that thermolysis of carbodiimides **15** (Scheme 1.5) in aromatic solvents is an efficient route to indoloquinolines **18** used as precursors for synthesizing naturally occurring alkaloids [31]. The cyclization is thought to occur through a two-step biradical Diels–Alder reaction that gives **17**, which then tautomerizes to **18**.



Scheme 1.5

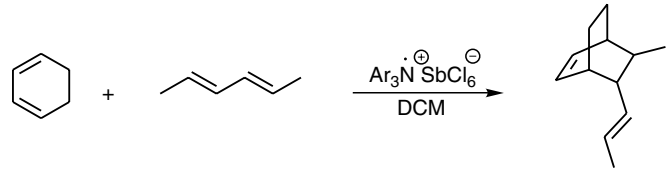
The reactivity of neutral dienophiles is greatly increased by converting them to the corresponding cation radicals because these highly electron-deficient species can then react readily with dienes.

The dimerization of 1,3-cyclohexadiene gives 30% adduct after 20 h at 30 °C [32]. In the presence of a catalytic amount of tris(*p*-bromophenyl) aminium hexachloroantimonate ($Ar_3N^{\bullet\oplus}SbCl_6^{\ominus}$; Ar = $pBrC_6H_4$) in CH_2Cl_2 at 0 °C, the cyclodimerization occurs in 15 min with 70% yield with a greater diastereoselectivity (*endo*/*exo* = 5:1) than that observed under thermal conditions (Equation 1.13) [33].



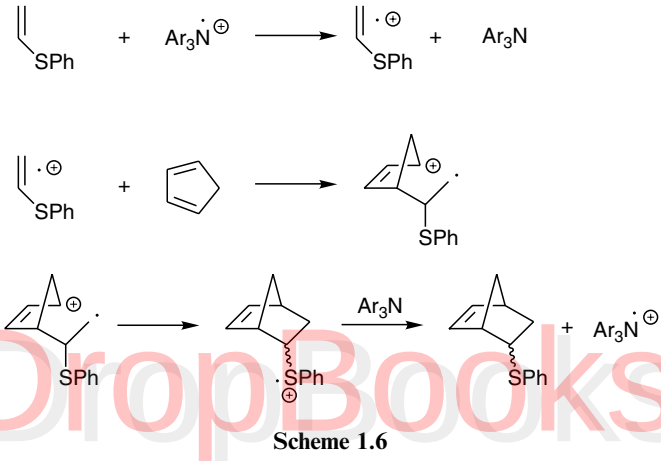
(1.13)

The first studies on cation-radical Diels–Alder reactions were undertaken by Bauld in 1981 who showed [33a] the powerful catalytic effect of aminium cation radical salts on certain Diels–Alder cycloadditions. For example, the reaction of 1,3-cyclohexadiene with *trans, trans*-2,4-hexadiene in the presence of $Ar_3N^{\bullet\oplus}$ is complete in 1 h and gives only the *endo* adduct (Equation 1.14) [33].



(1.14)

As a continuation of these studies, Bauld recently reported evidence of a stepwise mechanism in the cation-radical Diels–Alder reaction of phenyl vinyl sulfide with cyclopentadiene [34, 35] (Scheme 1.6).



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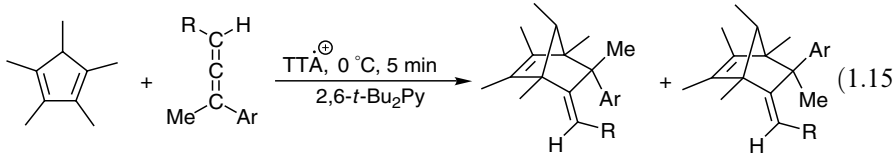
Scheme 1.6

An analogous stepwise mechanism was also proposed by Wöhrle [36] for the cation-radical-initiated cycloaddition of electron-rich allenes with pentamethylcyclopentadiene in the presence of tris (*p*-tolyl) aminium hexafluoroantimonate ($TTA^{\bullet\oplus}SbF_6^{\ominus}$) (Equation 1.15).

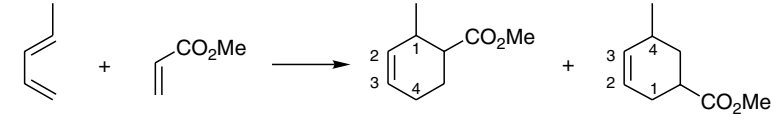


(1.15)

1.5 REGIOCHEMISTRY

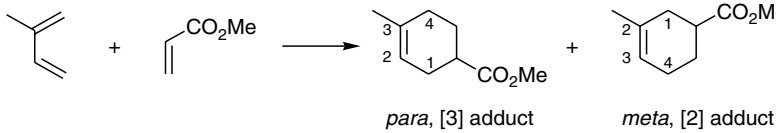
When an unsymmetrical diene reacts with an unsymmetrical dienophile, two regioisomer adducts can be formed depending on the orientation of the substituents in the adduct [37] (Equations 1.16 and 1.17).

The regioisomer adducts are usually named by using the classic nomenclature of disubstituted benzenes: *ortho*, *meta* and *para*. This descriptive method, however, encounters difficulties with adducts as simple as those from disubstituted dienes and dienophiles. Thus a new nomenclature has been proposed [38]. The original diene atoms forming the six-membered ring are numbered one through four, the lowest number being closest to the more electron-withdrawing group bonded to the atom of the original dienophile. The positional relationship of the substituents is now identified by a simple number set within a bracket followed by the word *adduct*.



ortho, [1] adduct *meta*, [4] adduct

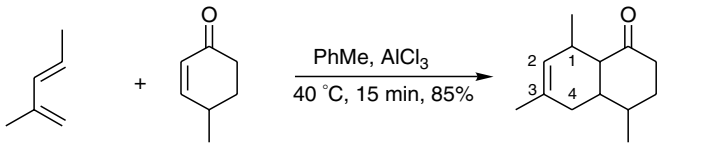
20 °C 90% 10%
20 °C, $AlCl_3$ 98% 2% (1.16)



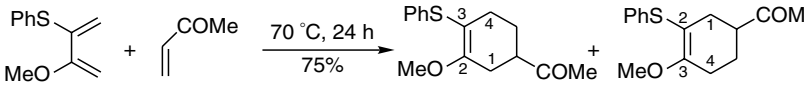
para, [3] adduct *meta*, [2] adduct

20 °C 70% 30%
20 °C, $AlCl_3$ 95% 5% (1.17)

The description of the regiochemistry of the cycloaddition products of dienes that have two or more dissimilar substituents may require incorporation of their name in the new notation (Equations 1.18 [38] and 1.19 [39]).



[1,3] adduct (1.18)



80% 20%
[2 (OMe), 3 (SPh)] [2 (SPh), 3 (OMe)] (1.19)

The regioselectivity of the Diels–Alder reaction depends on the number and nature of substituents on diene and dienophile and on the reaction conditions (catalyst, temperature, pressure, solvent, etc.). Generally, 1- and 2-substituted

butadienes react with monosubstituted dienophiles to give mainly *ortho* and *para* adducts, respectively. When two different substituents are present on the diene, one works as regiodirector and controls the regiochemistry of the reaction. Table 1.3 illustrates the main regioisomer obtainable in the cycloaddition of disubstituted 1,3-butadienes with monosubstituted ethenes [40] where R_1 is the regiodirector group. Thus, for example, in the cycloaddition of 2-methoxy-3-thiophenylbutadiene with methylvinylketone, one can foresee that the main regioisomer will be the 1-thiophenyl-2-methoxy-4-acetyl-cyclohexen-1-ene because the SPh is the regiodirector group. In fact, this regioisomer is the main reaction product (80%) [39].

Exceptions to the *ortho–para* rule have been observed, so the prediction of the regiochemistry is still a stimulating challenge.

The regioselectivity of simple Diels–Alder reactions has been explained on the basis of the electronic effects of the substituents which orient the attack of reagent species by generating partial positive and negative charges in the diene and dienophile. Generally, the more powerful the electronic effect of the substituents, the more regioselective the reaction. Although this explanation has some merit, the FMO theory [41] and the matching of complementary reactivity surfaces of the diene and dienophile [40] give a better explanation.

Table 1.3 Regioselectivity of Diels–Alder reactions of disubstituted 1,3-butadienes with monosubstituted ethenes ($RCH{=}CH_2$)

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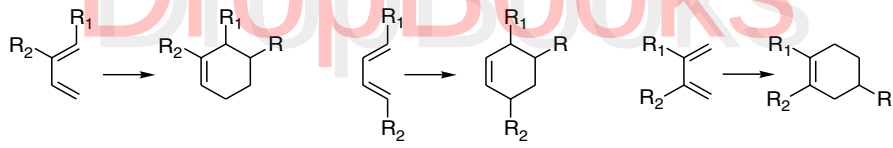
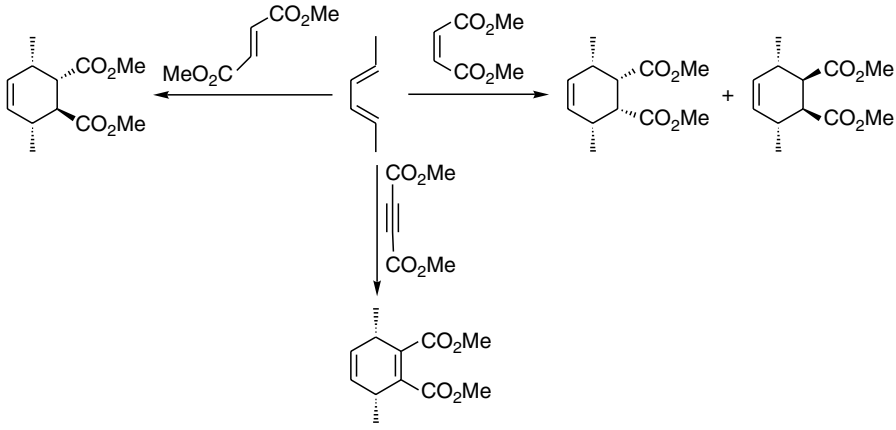


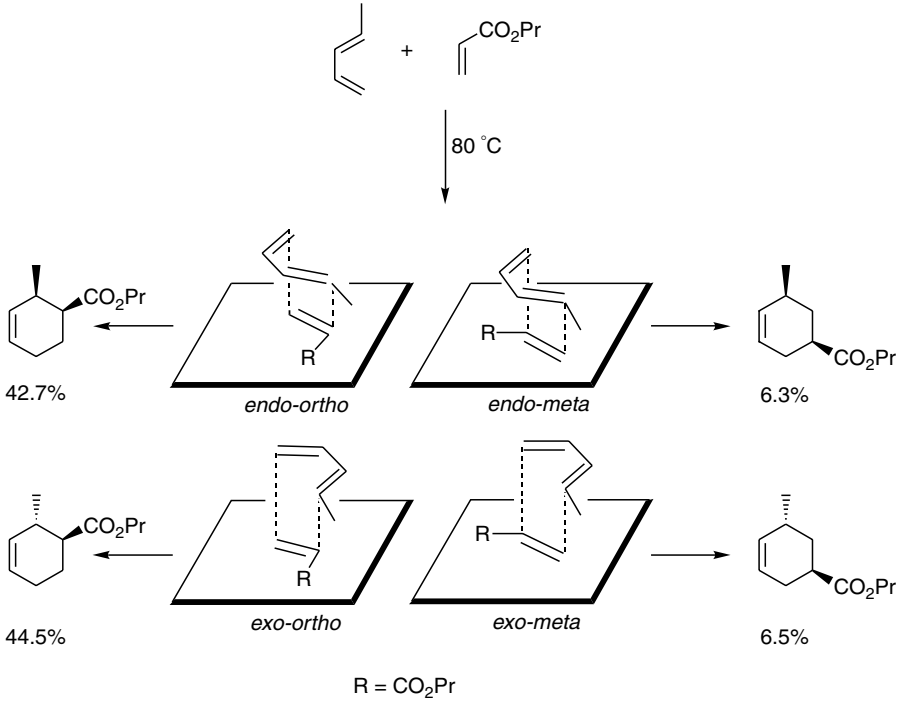
R_1	R_2	R_1	R_2	R_1	R_2
Me	Ph	Me	$SiEt_3$	Ph	Me
Me	OEt	Ph	Me	SPh	Me
Me	OAc	$NHCO_2Et$	Me	SPh	OMe
Me	Cl	$NHCO_2Bu$	SPh	SPh	OAc
Bn	$NHCOCH_3$	OAc	Et	Cl	Me
SPh	OMe	SPh	OAc		

1.6 STEREOCHEMISTRY

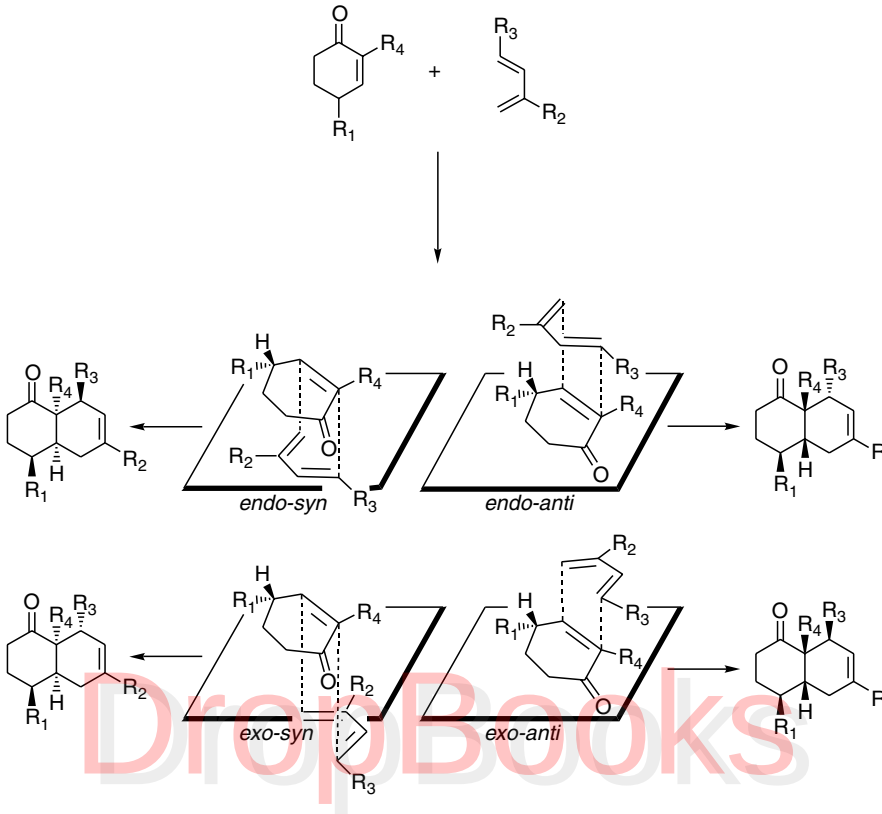
Pericyclic Diels–Alder reactions are suprafacial reactions and this manner of bond formation preserves in the cycloadduct the relative stereochemistry of the substituents at C_1 and C_4 and at C_1 and C_2 of the parents diene and dienophile, respectively (Scheme 1.7). The relative stereochemistry of the substituents in the



Scheme 1.7



Scheme 1.8



Scheme 1.9

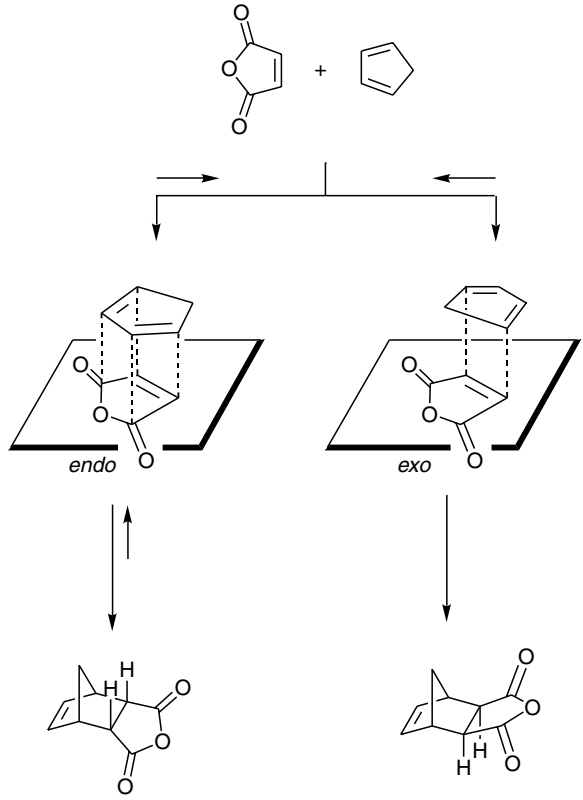
new stereogenic centers of the adduct is fixed by two possible suprafacial approaches named *endo* and *exo*. The *endo* mode of attack is the spatial arrangement of reactants in which the bulkier sides of the diene and dienophile lie one above the other, while in the *exo* mode of addition the bulkier side of one component is under the small side of the other. If one also considers the regioselectivity and the face selectivity of the reaction, a considerable number of isomers can, in principle, be produced. Schemes 1.8 and 1.9 give two general pictures. However, the Diels–Alder cycloaddition is known to be a highly selective reaction, and consequently only one or a very limited number of isomers are actually obtained.

The *exo* addition mode is expected to be preferred because it suffers fewer steric repulsive interactions than the *endo* approach; however, the *endo* adduct is usually the major product because of stabilizing secondary orbital interactions in the transition state (Scheme 1.10). The *endo* preference is known as Alder's rule. A typical example is the reaction of cyclopentadiene with maleic anhydride which, at room temperature, gives the *endo* adduct which is then converted at

200 °C to the thermodynamically more stable *exo* adduct through a retro Diels–Alder reaction followed by re-addition (Scheme 1.10).

The generally observed *endo* preference has been justified by secondary orbital interactions, [17e, 42, 43] by inductive or charge-transfer interactions [44] and by the geometrical overlap relationship of the π orbitals at the primary centers [45].

The *exo–endo* diastereoselectivity is affected by Lewis acid catalysts, and the ratio of two stereoisomers can be explained on the basis of the FMO theory [17e, 46].

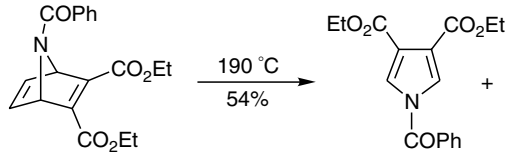


Scheme 1.10

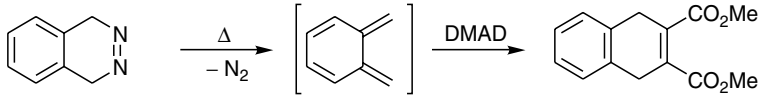
1.7 RETRO DIELS–ALDER REACTION

The Diels–Alder reaction is reversible and the direction of cycloaddition is favored because two π bonds are replaced by two σ-bonds. The cycloreversion occurs when the diene and/or dienophile are particularly stable molecules (i.e.

formation of an aromatic ring, of nitrogen, of carbon dioxide, of acetylene, of ethylene, of nitriles, etc.) or when one of them can be easily removed or consumed in a subsequent reaction (Equations 1.20 and 1.21).



(1.20)



(1.21)

The retro Diels–Alder reaction usually requires high temperatures in order to surmount the high activation barrier of the cycloreversion. Moreover, the strategy of retro Diels–Alder reaction is used in organic synthesis to mask a diene fragment or to protect a double bond [47]. Some examples are illustrated in Scheme 1.11.

The retro Diels–Alder reaction is strongly accelerated when an oxide anion substituent is incorporated at positions 1 and 2 of the six-membered ring which has to be cycloreversed, namely at one terminus carbon of the original diene or at one sp^2 carbon of the dienophile [51] (Equation 1.22).

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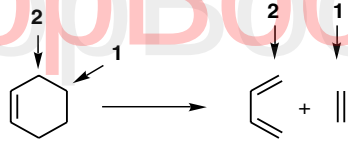
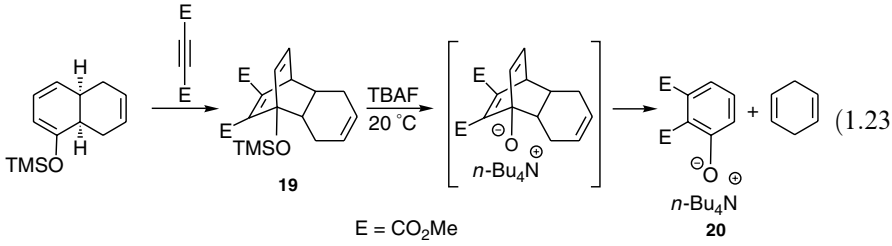


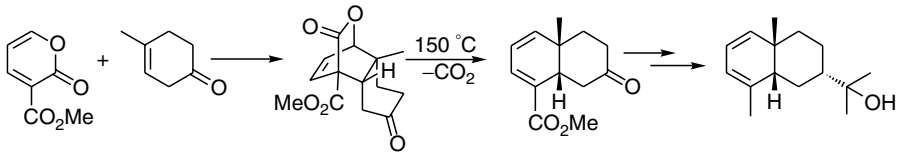
(1.22)

The first example of an oxide-anion accelerated retro Diels–Alder reaction was reported by Papies and Grimme [52]. The adduct **19** (Equation 1.23) treated with tetra-*n*-butylammonium fluoride (TBAF) in THF at room temperature is immediately converted into **20**, in contrast to the parent **21** (Equation 1.24) which undergoes cycloreversion into **22** at 100 °C. The dramatic oxide-anion acceleration (> 10^6) was ascribed to the loss of basicity of about 8 pK_b units in the transformation of alcoholate ion of precursor **19**

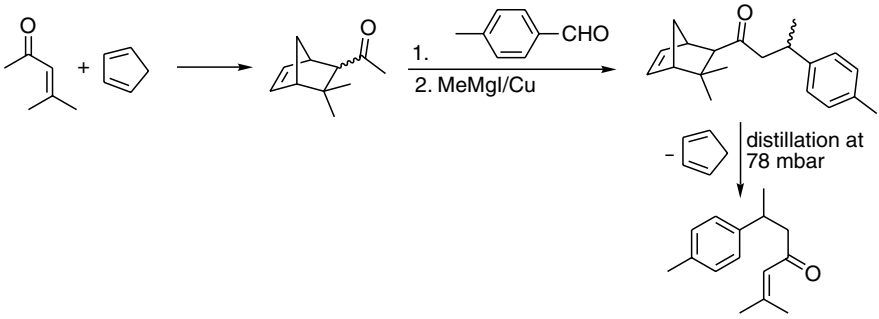


(1.23)

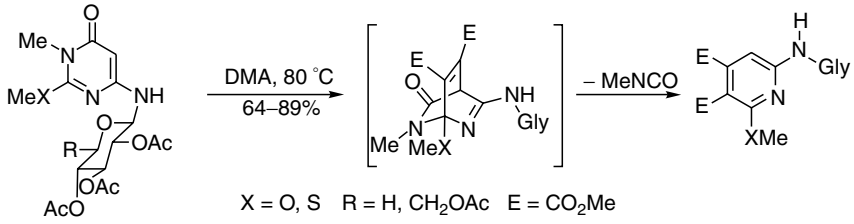
Synthesis of (±)-occidentalol [48]



Synthesis of (±)-turmerone [49]

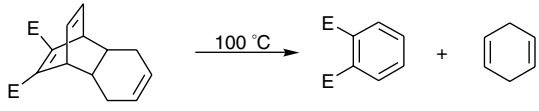


Synthesis of 2-glycosylamino pyridines [50]



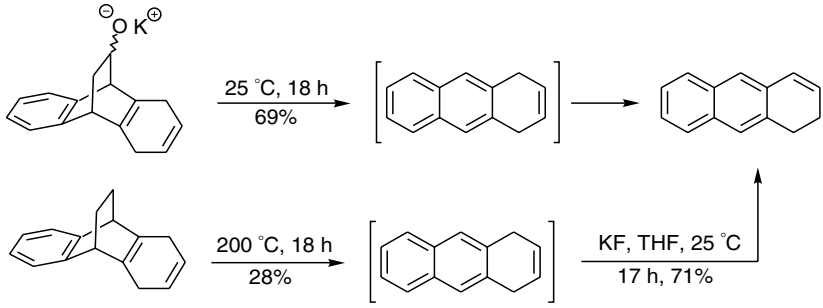
Scheme 1.11

into the phenolate ion of the product **20**. This is an example of acceleration of retro Diels–Alder when an oxide substituent is incorporated at the terminus of the 4π component of the Diels–Alder adduct, that is, position 2 in the model of Equation 1.22.



21 **22** (1.24)

An example of the effect of oxide-anion associated with the 2π component (i.e. position 1, Equation 1.22) is illustrated in Equation 1.25 [53]. The potassium salt of 1,4-dihydro-11-hydroxy-9,10-dihydro-9,10-ethanoanthracene undergoes more facile debridging (remotion of ethylene) than the 11-deoxygenated parent compound.



(1.25)

1.8 *HOMO*-DIELS–ALDER REACTION

The reaction of a diene having the two double bonds separated by a sp^3 center with a dienophile to give a $[2\pi + 2\pi + 2\pi]$ cycloaddition is called a *homo-Diels–Alder* reaction. Since the diene is not conjugated, a σ bond is created in lieu of a double bond. In principle, an open-chain diene gives rise to a central-bridged six-membered ring, while an inner-ring diene produces a bridged six-membered ring fused with a ring whose size depends on the size of the starting cyclodiene (Equations 1.26 and 1.27). Norbornadienes are the dienes most often used to investigate the *homo*-Diels–Alder reaction.

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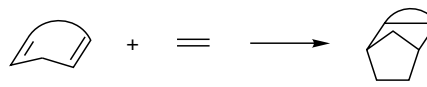
(1.26)

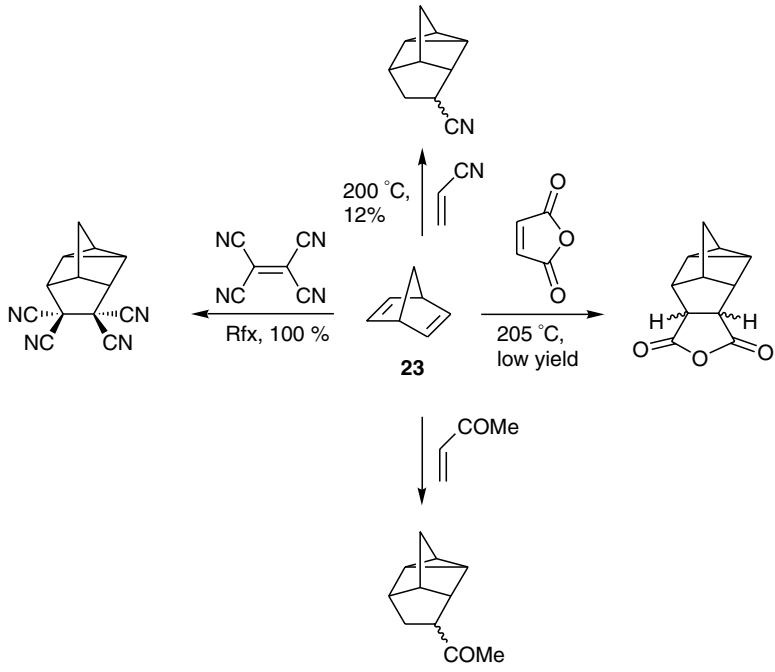


(1.27)

A minority of authors use the term *homo* not to indicate the relative position of the two double bonds of diene involved in the reaction, but to emphasize that the six-membered adduct is formed by all carbons [54].

The cycloaddition between norbornadiene (**23** in Scheme 1.12) and maleic anhydride was the first example of a *homo*-Diels–Alder reaction [55]. Other venerable examples are reported in Scheme 1.12 [56]. Under thermal conditions, the reaction is generally poorly diastereoselective and occurs in low yield, and therefore several research groups have studied the utility of transition metal catalysts [57]. Lautens and coworkers [57c] investigated the cycloaddition of norbornadiene and some of its monosubstituted derivatives with electron-deficient dienophiles in the presence of nickel-cyclooctadiene $Ni(COD)_2$ and PPh_3. Some results are illustrated in Tables 1.4 and 1.5.

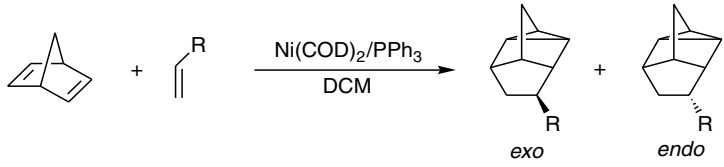
The mechanism of metal-catalyzed *homo*-Diels–Alder reaction proposed by Noyori [57c, 58] requires the coordination of double bonds of diene and



Scheme 1.12

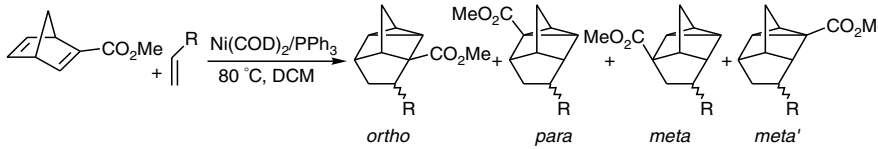
dienophile to the metal followed by the formation of metallocyclobutane which is converted to metallocyclohexane and then to the cycloadduct (Scheme 1.13).

Table 1.4 $Ni(COD)_2/PPh_3$ catalyzed *homo*-Diels–Alder reaction of norbornadiene with electron-deficient dienophiles

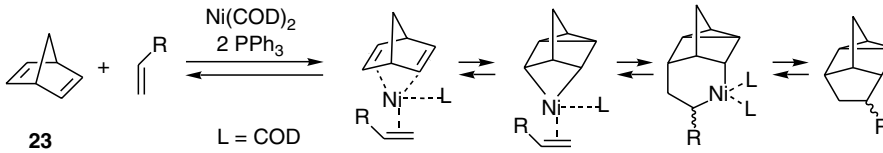


R	*T*(°C)	*exo/endo*	Yield (%)
COMe	80	>20	99
CHO	20	3	58
CO*t*-Bu	60	1.5	69
CN	80	4	82
SO_2Ph	20	1	75
SOPh	20	7	65

Table 1.5 $Ni(COD)_2/PPh_3$ catalyzed *homo*-Diels–Alder reactions of 2-carboxyethyl-norbornadiene with electron-deficient dienophiles



R	*ortho* (*exo*/*endo*)	*para* (*exo*/*endo*)	*meta* (*exo*/*endo*)	*meta′* (*exo*/*endo*)	Yield (%)
CN	0	100 (1:2.3)	0	0	94
SO_2Ph	0	66 (>20)	0	33 (>20)	75
COMe	20 (0:1)	70 (3)	0	10 (1:1.4)	84



Scheme 1.13

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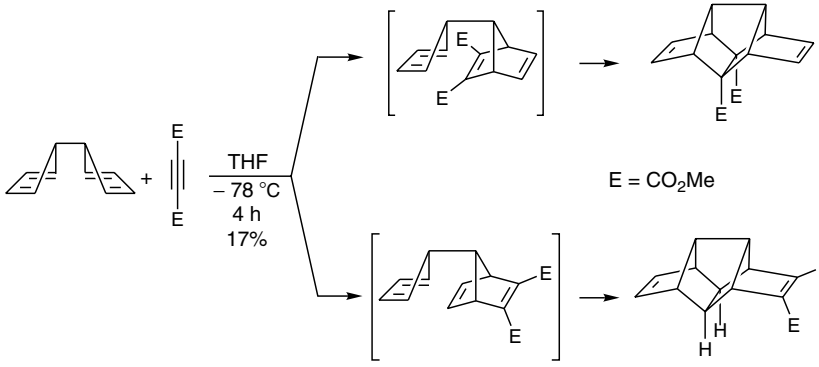
1.9 MULTIPLE DIELS–ALDER REACTION

Processes consisting of two or more synthetic steps carried out in the same flask without isolating any intermediates have been widely investigated in the last decade due to their ecological and economic advantages when compared to a stepwise procedure. In this respect the Diels–Alder reaction is a frequent example.

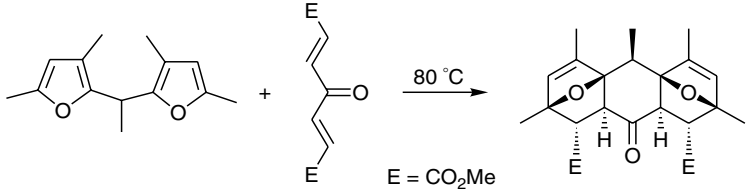
The one-pot multistep process has been named in various ways: domino, cascade, tandem, timed, consecutive, transmissive, etc. Sometimes the word used does not describe the real meaning of the procedure in that there is no conformity between the customary use of the term and the chemical transformation. These terms were recently defined more pertinently [59].

A domino Diels–Alder reaction (the term was chosen from the well-known game) is a one-pot process involving two or more Diels–Alder reactions carried out under the same reaction conditions without adding additional reagents or catalyst such that the second, third, etc., cycloaddition is the consequence of the functionality generated in the previous reaction. A historical example is illustrated in Equation 1.28 [60]. This type of transformation is sometimes named tandem or cascade, but these terms seem less appropriate for describing a time-resolved transformation.

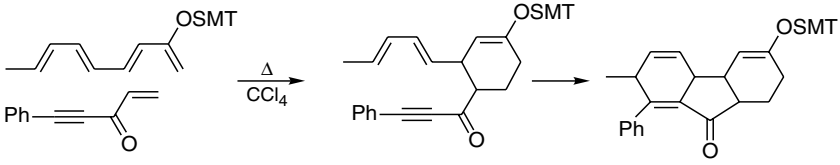


(1.28)

A tandem Diels–Alder reaction (the term refers to two operating units that are distinct but working at the same time) would indicate a process involving two distinct Diels–Alder reactions working at the same time (Equation 1.29) [6], and a cascade Diels–Alder reaction would refer to a transformation involving at least two Diels–Alder reactions occurring in sequence, without any reference to the fact that the subsequent reaction is the consequence of the functionality generated in the previous reaction (Equation 1.30) [61].

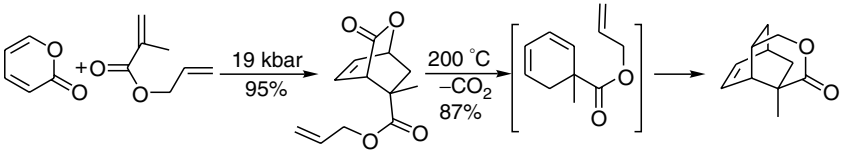


(1.29)

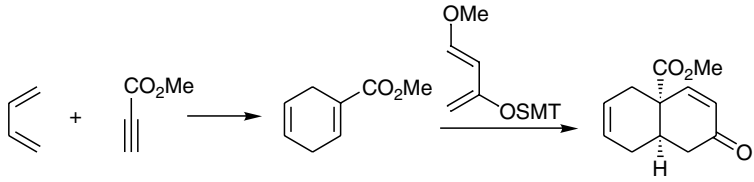


(1.30)

A consecutive or timed Diels–Alder reaction is a one-pot process in which the first Diels–Alder does not promote the second, so it is necessary to change the experimental conditions or add reagents to allow the successive cycloadditions (Equations 1.31 [62] and 1.32 [63]).



(1.31)



(1.32)

Sometimes it is difficult to classify a one-pot multi-step process. Thus for the sake of clarity, we think that the more general term *multiple reaction* is preferable to indicate a one-pot process in which several bonds are formed sequentially, regardless of whether the reaction conditions are changed or not, or whether new reagents are added during the process.

1.10 THEORY

According to frontier molecular orbital theory (FMO), the reactivity, regiochemistry and stereochemistry of the Diels–Alder reaction are controlled by the suprafacial *in phase* interaction of the highest occupied molecular orbital (HOMO) of one component and the lowest unoccupied molecular orbital (LUMO) of the other. [17e, 41–43, 64] These orbitals are the closest in energy; Scheme 1.14 illustrates the two dominant orbital interactions of a symmetry-allowed Diels–Alder cycloaddition.

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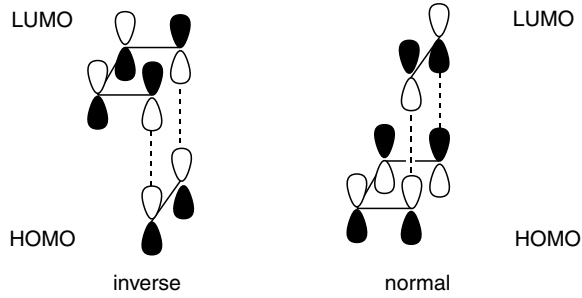
1.10.1 Reactivity and Substituent Effects

The reactivity of a Diels–Alder reaction depends on the HOMO–LUMO energy separation of components: the lower the energy difference, the lower is the transition state energy of the reaction. Electron-withdrawing substituents lower the energy of both HOMO and LUMO, while electron-donating groups increase their energies. HOMO diene-controlled Diels–Alder reactions (Scheme 1.14) are accelerated by electron-donating substituents in the diene and by electron-withdrawing substituents in the dienophile



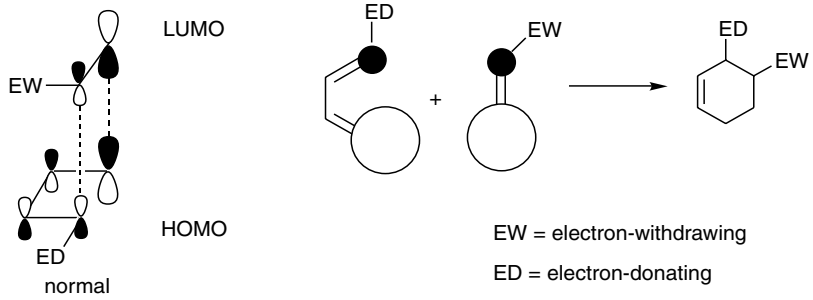
Scheme 1.14

(normal electron-demand Diels–Alder reaction). LUMO diene-controlled Diels–Alder reactions are influenced by electronic effects of the substituents in the opposite way (inverse electron-demand Diels–Alder reaction). The neutral electron-demand Diels–Alder reaction is HOMO–LUMO-diene controlled and is insensitive to substituents in either the diene or the dienophile.

Lewis acids can greatly accelerate the cycloaddition. Instructive examples are the $AlCl_3$-catalyzed reaction of cycloalkenones with 1,3-butadienes [12]. The catalytic effect is explained by FMO theory considering that the coordination of the carbonyl oxygen by Lewis acid increases the electron-withdrawing effect of the carbonyl group on the carbon–carbon double bond and lowers the LUMO dienophile energy.

1.10.2 Regioselectivity

The *ortho–para* rule is explained by FMO theory on the basis of the orbital coefficients of the atoms forming the σ-bonds. The regiochemistry is determined by the overlap of the orbitals that have larger coefficients (larger lobes in Scheme 1.15). The greater the difference between the orbital coefficients of the two end atoms of diene and two atoms of dienophile, which form the two σ-bonds, the more regioselective the cycloaddition.



Scheme 1.15

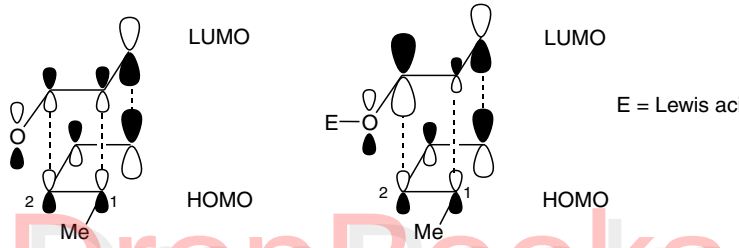
Lewis-acid-catalyzed cycloadditions of dienophiles, such as α,β-unsaturated carbonyl compounds, with open-chain carbon-dienes, are generally highly *ortho–para* regioselective because the oxygen complexation increases the difference of LUMO coefficients of the alkene moiety.

The orbital interaction depicted in Scheme 1.15 shows that the two σ-bonds form at the same time but do not develop to the same extent. The Diels–Alder cycloaddition of unsymmetrical starting materials is therefore concerted but asynchronous. A highly unsymmetrical diene and/or dienophile give rise to a highly unsymmetrical transition state and a stepwise pathway can be followed.

A concerted and synchronous Diels–Alder reaction occurs only with symmetric nonpolar reagents.

1.10.3 Stereoselectivity

The FMO theory explains the kinetically favored *endo* approach considering an additional nonbonding interaction. This secondary orbital interaction does not give rise to a bond but contributes to lowering the energy of the *endo* transition state with respect to that of the *exo* one. The larger are the lobes of interacting orbitals, the better is the overlap, the stronger is the interaction, and the more favored is the formation of *endo* adduct. In the cycloaddition between piperylene and acrolein (Scheme 1.16), the secondary orbital interaction occurs between the C-2 of the diene and the carbonyl carbon of the dienophile.



Scheme 1.16

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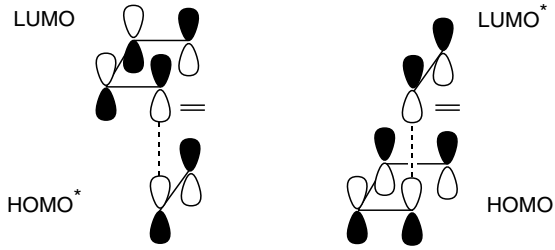
The complexation with Lewis acids or the protonation influences both the energy and the coefficients of carbon atoms of the LUMO orbital of the dienophile. The coefficient of the carbonyl carbon orbital increases (Scheme 1.16); consequently, the stabilizing effect of the secondary orbital interaction is greatly increased and the *endo* addition is more favored.

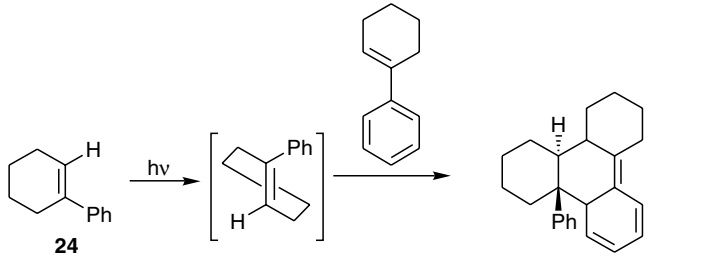
The stereochemistry of substituents at C-1 and C-4 of the diene and that of substituents at C-1 and C-2 of the dienophile are preserved in the cycloadduct because the Diels–Alder is a concerted reaction that takes place suprafacially on both components.

In a photochemical cycloaddition, one component is electronically excited as a consequence of the promotion of one electron from the HOMO to the LUMO*. The HOMO*–LUMO* of the component in the excited state interact with the HOMO–LUMO orbitals of the other component in the ground state. These interactions are bonding in [2+2] cycloadditions, giving an intermediate called exciplex, but are antibonding at one end in the $[_{\pi}4_s +_{\pi} 2_s]$ Diels–Alder reaction (Scheme 1.17); therefore this type of cycloaddition cannot be concerted and any stereospecificity can be lost. According to the Woodward–Hoffmann rules [65], a concerted Diels–Alder reaction is thermally allowed but photochemically forbidden.

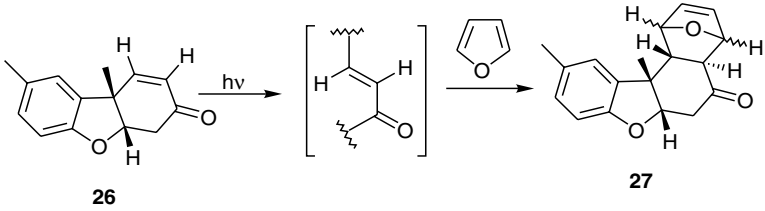


Scheme 1.17

Stable *cis*-1-phenyl-1-cyclohexene **24** photodimerizes via Diels–Alder cycloaddition to *trans* adduct **25** (Equation 1.33) [66] and the photoexcitation of dihydrobenzofuran-fused cyclohexenone **26** in net furan gives the *trans* fused Diels–Alder adduct **27** (Equation 1.34) [67].



(1.33)



(1.34)

The non-preservation of *cis* stereochemistry of dienophiles **24** and **26** in the adducts **25** and **27** is due to a *cis–trans* photoisomerization of the double bond and to the concerted suprafacial Diels–Alder cycloaddition of diene to the ground state of *trans* dienophiles.

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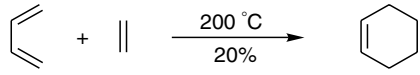
2 Thermal Diels–Alder Reaction

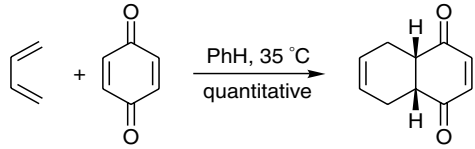
2.1 INTRODUCTION

From 1928 when Otto Diels and Kurt Alder [1] made their extraordinary discovery until 1960 when Yates and Eaton [2] reported the acceleration of the Diels–Alder cycloadditions by Lewis acid catalysts, these reactions were essentially carried out under thermal conditions owing to the simplicity of the accomplishing thermal process. Since then a variety of methods have been developed to accelerate the reactions. The reaction between 1,3-butadiene and ethylene (Equation 2.1) is a typical example of a thermal Diels–Alder cycloaddition.



(2.1)

Since the reactivity depends on the lowest HOMO–LUMO energy separation that can be achieved by the reacting partners, all the factors, steric and electronic, that lower the HOMO–LUMO distance increase the reaction rate and, as a consequence, allow the reactions to be carried out under mild conditions. Thus the normal electron-demand Diels–Alder reaction between 1,4-benzoquinone and 1,3-butadiene (Equation 2.2) proceeds at 35 °C almost quantitatively.



(2.2)

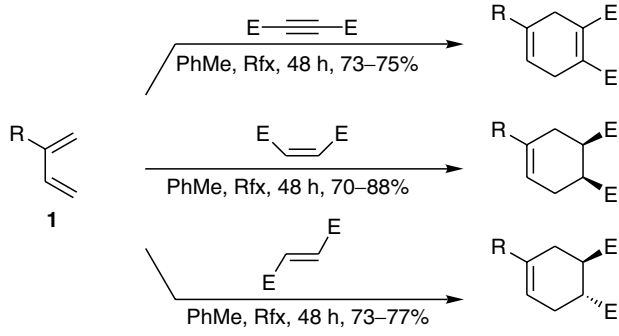
There are many types of Diels–Alder reactions that are carried out under thermal conditions. This chapter will deal with the most significant developments, the potential and range of applications of this methodology of both the intermolecular and intramolecular cycloadditions in organic synthesis.

2.2 CARBON DIELS–ALDER REACTIONS

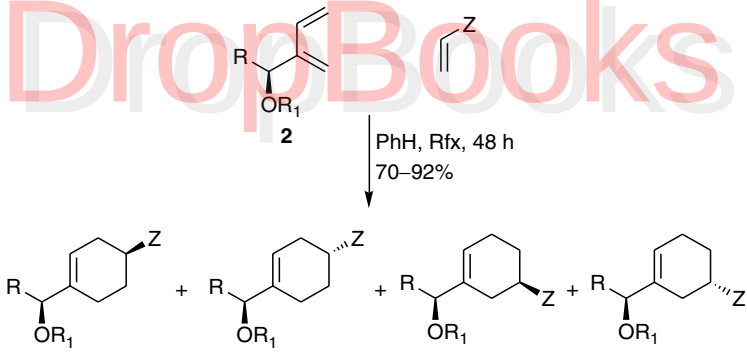
2.2.1 Open-Chain Dienes

Highly functionalized cyclohexenes have been prepared by Diels–Alder reactions of butadienes **1** (Scheme 2.1) and chiral butadienes **2** (Scheme 2.2) with

various dienophiles [3,4]. Good regio- and facial selectivities were observed with dienes **2** bearing a free hydroxy group; when this group was protected the stereoselectivity was reversed and lowered. When the chiral dienes **3,** bearing

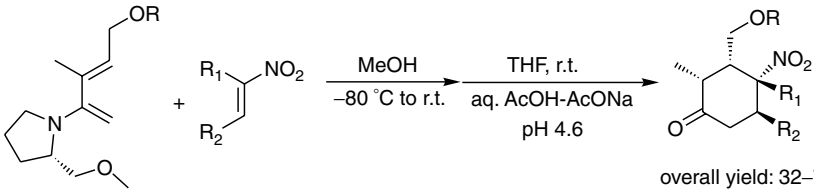


Scheme 2.1



Scheme 2.2

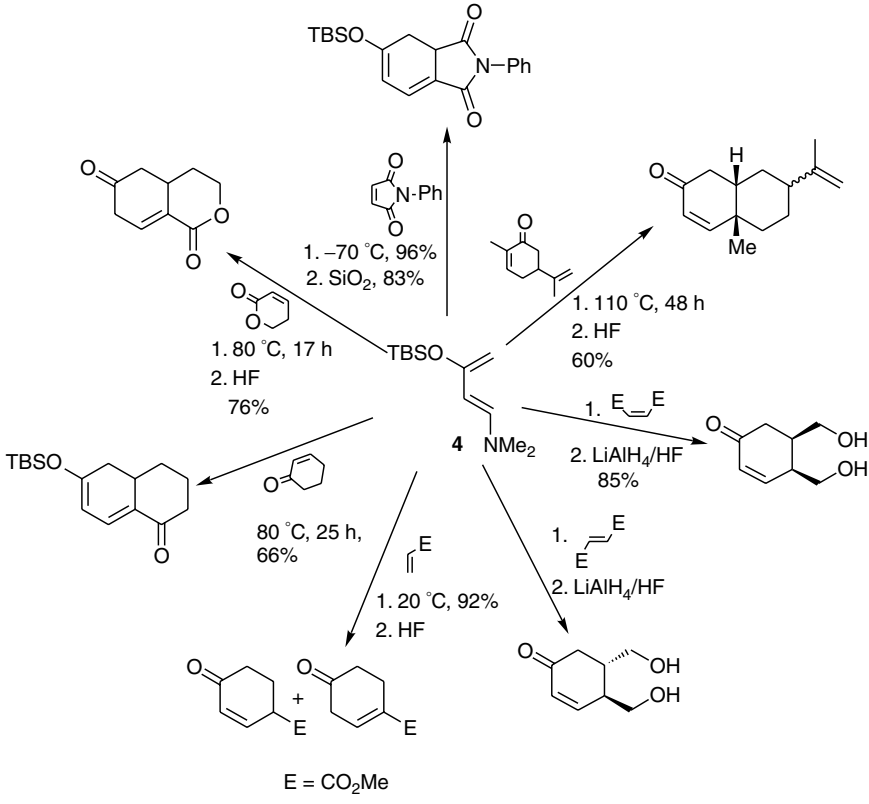
an S-(+)-2-methoxymethyl pyrrolidine as chiral auxiliary, were used to react with nitroalkenes, a variety of optically active cyclohexanones [5] were obtained (Equation 2.3). The cycloadditions were highly diastereoselective, showed a high level (92–95 %) of enantiomeric excess and, after hydrolysis of the cycloadducts, furnished optically active nitrocyclohexanones.



(2.3)

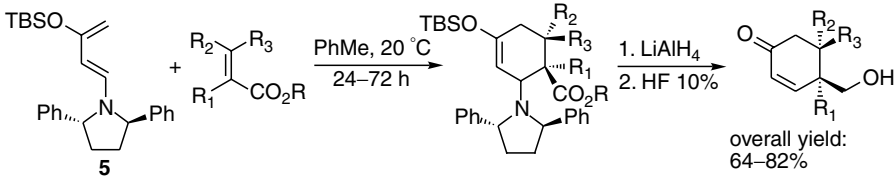
R = Me, OMOM, TBDMS;
R_1 = H, Me;
R_2 = H, Me, CH_2OBn, *i*-Pr, Ph, 2-Fu, 3-Fu, o-Cl-C_6H_4, *p*-OMe-C_6H_4, *p*-NO_2-C_6H_4;
R_1-R_2 = $-(CH_2)_4-$

Conjugated cyclohexenones [6] have also been easily prepared by combining the cycloaddition of dimethylaminobutadiene **4** and several cyclic and acyclic dienophiles followed by the elimination of the amino group from the cycloadducts under acidic conditions. Scheme 2.3 summarizes some of these results.



Scheme 2.3

This type of diene is also interesting because the amino substituents open up the possibility of using chiral amines, thus allowing optically active conjugated cyclohexenones to be synthesized. An example is the chiral aminosiloxy diene **5** which reacts with several dienophiles leading to cycloadducts that were directly converted into chiral cyclohexenones [7] (Scheme 2.4) with fairly good yield (64–82%) and high enantiomeric excess (86–98%). The amino functionality can also be retained [8] as shown by the Diels–Alder reactions of 2-aminomethylbutadienes **6** (Equation 2.4) with a variety of dienophiles (dimethylfumarate, dimethylmaleate, methylacrylate, ethylacrylate and dimethylacetylenedicarboxylate).



R = Me, Et, *t*-Bu; R_1 = H, Et; R_2, R_3 = Ph, CO_2Me, CO_2Et

Scheme 2.4

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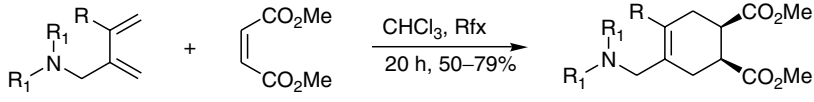
A one-pot procedure [9] based on the cycloaddition of 4-aryl-2-silyloxybutadienes **7** and bisdiene **8** with alkynes, followed by oxidative aromatization of the cycloadducts, opened a route to polycyclic phenols without isolating the cyclohexadiene derivative intermediates (Scheme 2.5).

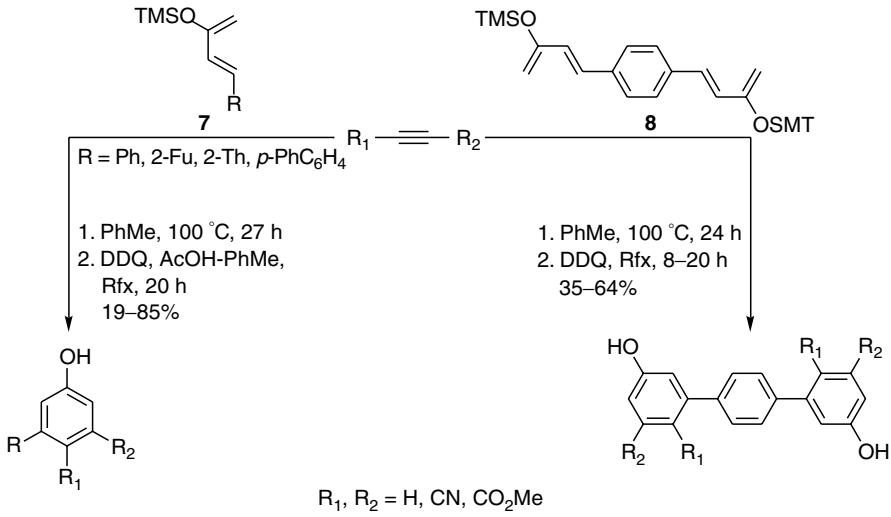


(2.4)

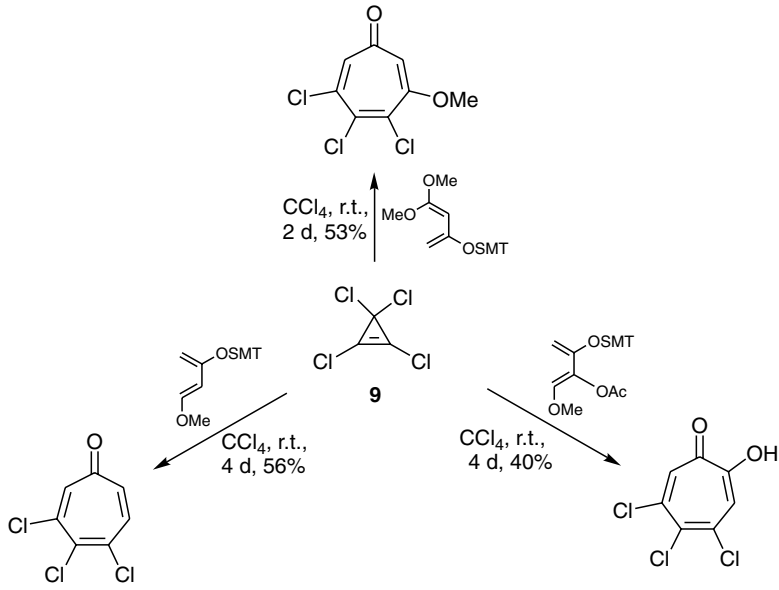
R = H, CH_2NMe_2; R_1 = Me, Et

The synthesis of halogen-containing organic substrates is currently a stimulating challenge for synthetic chemists. Among the many procedures that have been developed, Diels–Alder methodology has also been successfully used.

Trichlorinated tropones [10] have been prepared by a one-pot procedure based on thermal cycloaddition of tetrachlorocyclopropene **9** with electron-rich butadienes (Scheme 2.6) followed by spontaneous ring-expansion/dehydrochlorination of the resulting cycloadducts.

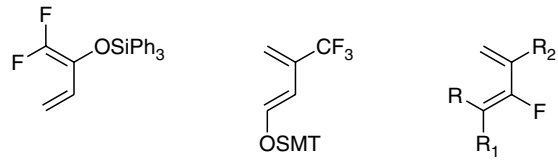


Scheme 2.5



Scheme 2.6

Aromatic fluoro-compounds have been prepared by thermal cycloaddition of fluorinated 1,3-butadienes **10–12** (Figure 2.1) with several dienophiles. Fluorophenols were obtained by cycloaddition of diene **10** with quinones [11]



10 **11** **12**

R, R_1, R_2 = H, Me, OMe, OSMT

Figure 2.1

(Scheme 2.7). The phenols were formed during isolation (chromatography on silica gel) from the corresponding cycloadducts. In the reaction with *p*-benzoquinone, a product was unexpectedly obtained from a *hetero*-Diels–Alder reaction with the quinone acting as a carbonyl dienophile.

The Diels–Alder reactions of dienes **11** and **12** with many dienophiles allowed other fluorinated aromatics to be synthesized [12,13]. For example, diene **11** reacted with dimethylacetylenedicarboxylate and ethylpropiolate (Scheme 2.8) to give trifluoromethyl diethylphthalate and trifluoromethylethylbenzoate, and diene **12** with *p*-benzoquinone affords 5-fluoronaphthoquinone (Equation 2.5).

Vinyl- and acetylenic tricarbonyl compounds are reactive dienophilic components in Diels–Alder reactions. Cycloadditions of these compounds with substituted butadienes were recently used to develop a new synthetic approach to indole derivatives [14] (Scheme 2.9) by a three-step procedure including (i) condensation with primary amines, (ii) dehydration and (iii) DDQ oxidation.

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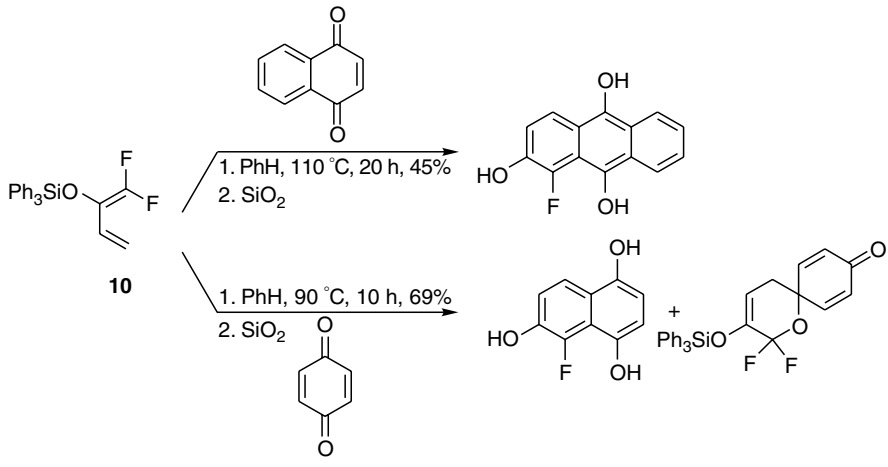
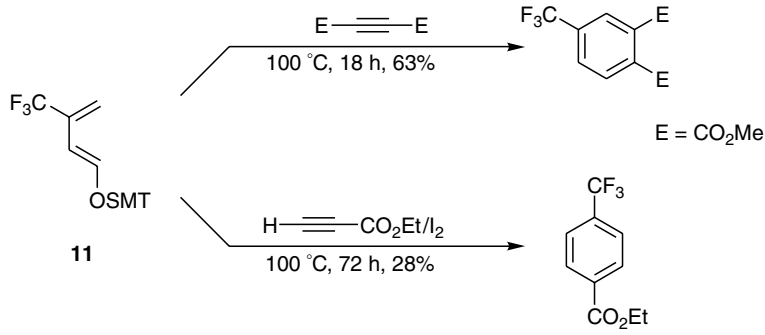
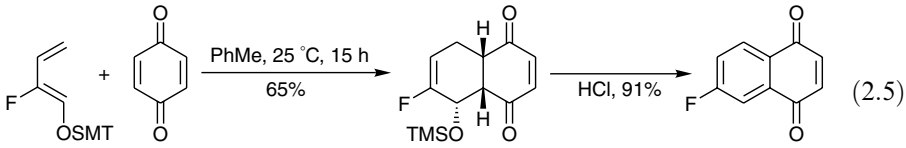


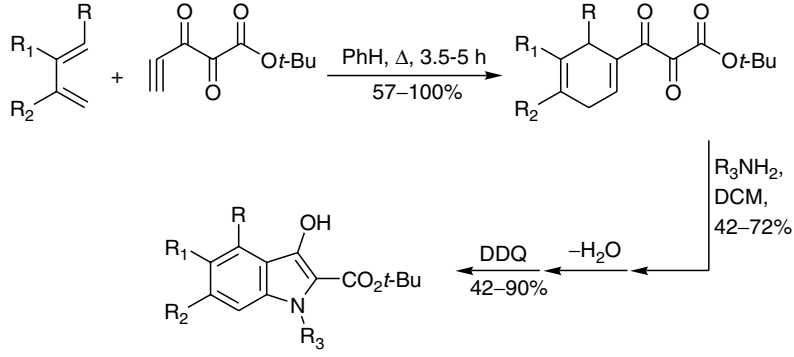
Scheme 2.7



Scheme 2.8



(2.5)

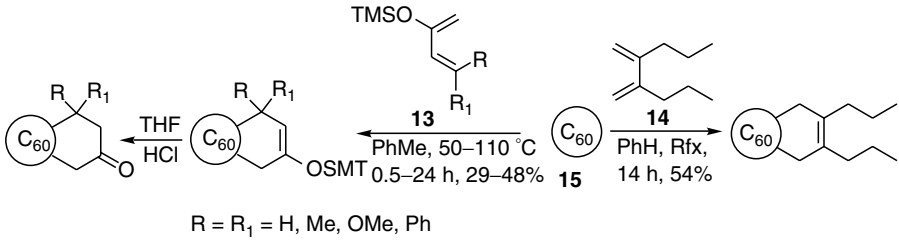


R, R_1, R_2 = H, Me, CH_2CO_2Et; R_3 = *n*-Bu, Bn

Scheme 2.9

Diels–Alder cycloaddition reactions are among the most common and expeditious methods for the derivatization of [60]-fullerene which acts as a good dienophile reacting with a wide variety of dienes bearing electron-donating and electron-withdrawing groups. Since cycloadducts undergo a facile retro-Diels–Alder reaction, the stability of the cycloadducts was attained either by incorporating the forming double bond into an aromatic ring or by a smooth conversion of the formed double bond into a single bond.

Diels–Alder reactions of butadienes **13** and 2,3-di-*n*-propylbutadiene **14** with [60]-fullerene **15** led to several fullerene derivatives [15–17] (Scheme 2.10). Dienes **13** and **14** bore electron-donating groups, but the reactions also occurred with electron-withdrawing substituents due to the sufficiently low-energy LUMO of C_{60}.



Scheme 2.10

Vinylboranes, a class of highly reactive dienophiles that has been explored by Singleton and coworkers [18–21], have been used to synthesize a wide variety of cyclohexenols, cyclohexenediols and bridgehead bicyclic alcohols by Diels–Alder reaction with a wide range of acyclic dienes. The alcohols are obtained by an oxidative H_2O_2/NaOH work-up of the intermediate borane adducts; by adding triethylamine before proceeding with oxidation, the protodeboronation side- reaction was eliminated and alcohols were obtained in good to excellent yields. Vinylborane can be readily prepared by metal–metal exchange of boron halides with vinyltin derivatives. While 9-vinyl-borabicyclo [3.3.1]nonane **(18)** is unstable and was therefore generated *in situ* and trapped by dienes, the *trans*-1,2-bis(catecholboryl)ethylene **(19)** is an air-stable crystalline solid [19]. The cycloadditions of numerous vinylboranes have been studied and some significant examples are summarized in Equations 2.6 and 2.7 and Scheme 2.11. Generally, the cycloaddition reactions have shown high regioselectivity and endo-diastereoselectivity.

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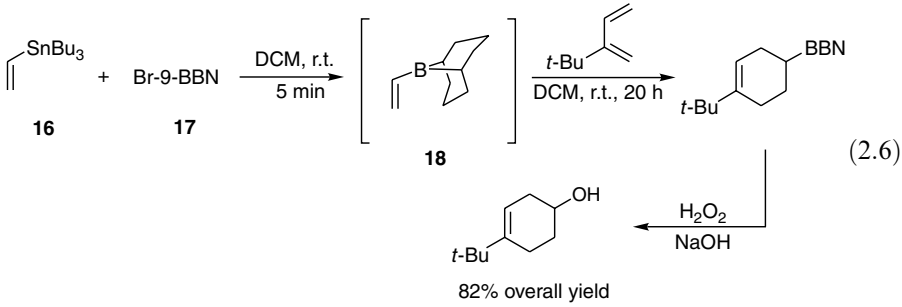

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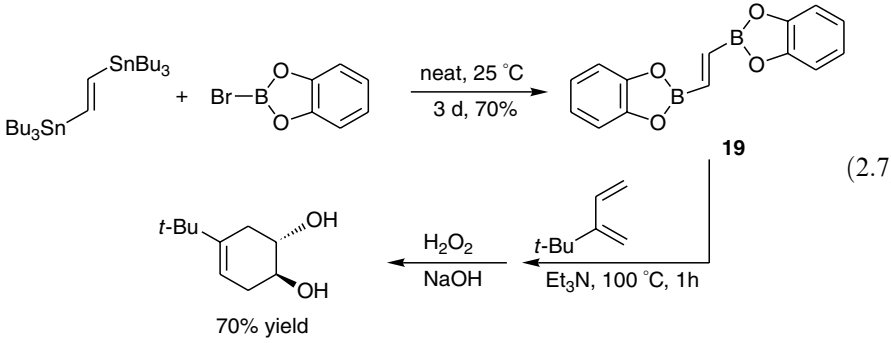
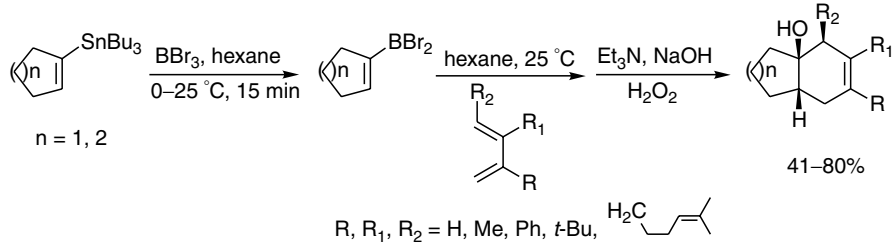


(2.7)



Scheme 2.11

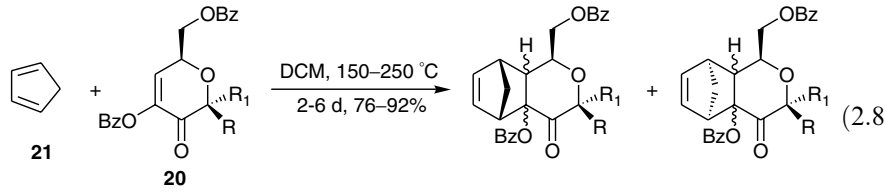
2.2.2 Cyclopentadienes and Cyclohexadienes

Cyclopentadienes and cyclohexadienes are versatile dienes that are commonly used to study mechanistic, regio- and stereochemical aspects of the Diels–Alder reaction and for synthetic purposes.

Cycloaddition reactions of homochiral dihydropyranones **20**, readily accessible from D-glucose, with cyclopentadiene **21** give optically active tetrahydrobenzopyranones bearing several stereogenic centers. The reactions of these poorly reactive dienophiles were carried out under drastic thermal, Lewis-acid catalyzed, high pressure conditions [22]. Although mixtures of four diastereoisomers (*endo/exo* and *syn/anti*) were always obtained, the highest yields and stereoselection were observed under thermal (Equation 2.8) and, especially, high pressure conditions (15 kbar, 25 °C, 2 d).

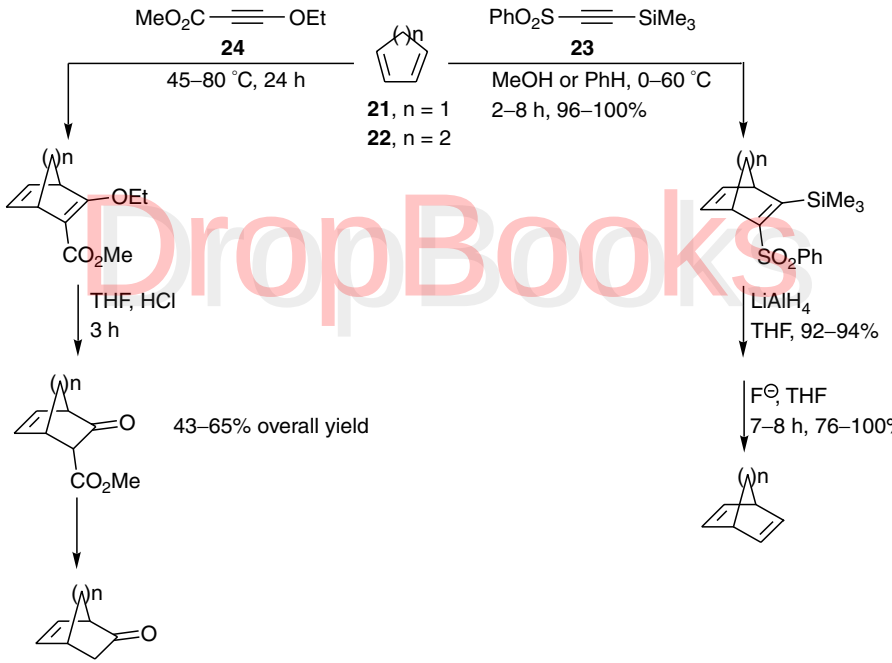
Norbornadienes, norbornenones and their homologs have been prepared [23, 24] by cycloaddition of cyclopentadiene **(21)** and cyclohexadiene **(22)** with 1-benzenesulfonyl-2-trimethylsilylacetylene **(23)** and 1-ethoxy-2-carbomethoxyacetylene **(24)**. Both were efficient dienophiles in the cycloaddition processes and dienophile **23** acted as an effective acetylene equivalent (Scheme 2.12). Norbornanes and their homologs can also be attained by Diels–Alder reaction

of dienes **21**, **22** and fulvene **25** with acetoxymaleic anhydride **(26)**, a reactive dienophile, which behaves like a ketene equivalent [25] (Scheme 2.13).



R = R_1 = H, OMe, OBz

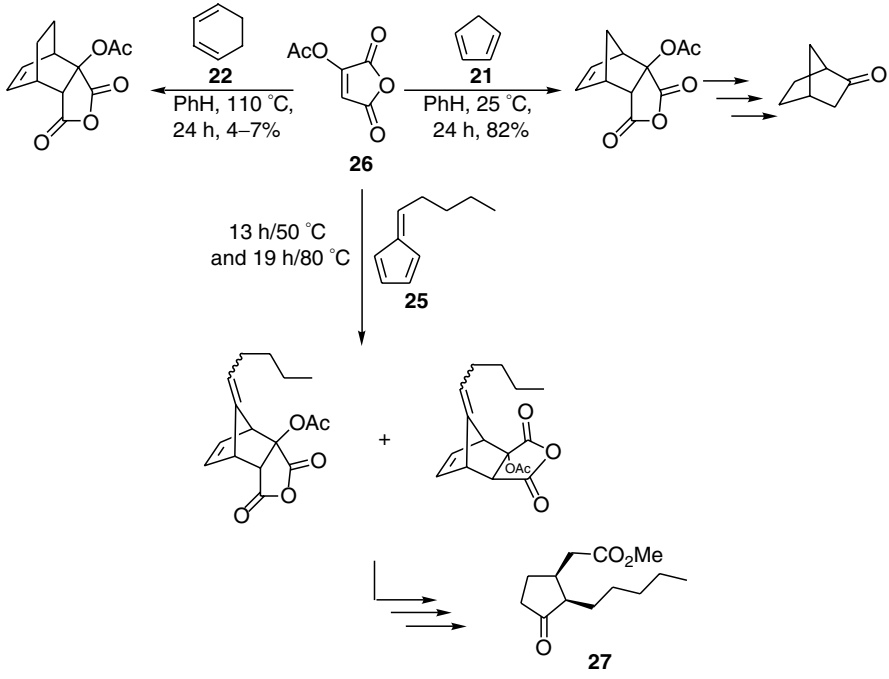
The cycloaddition between **25** and **26** is a crucial step for the synthesis of methyl *cis*-dihydrojasmonate, a key constituent of the commercial jasmine fragrance Hedione **27**.



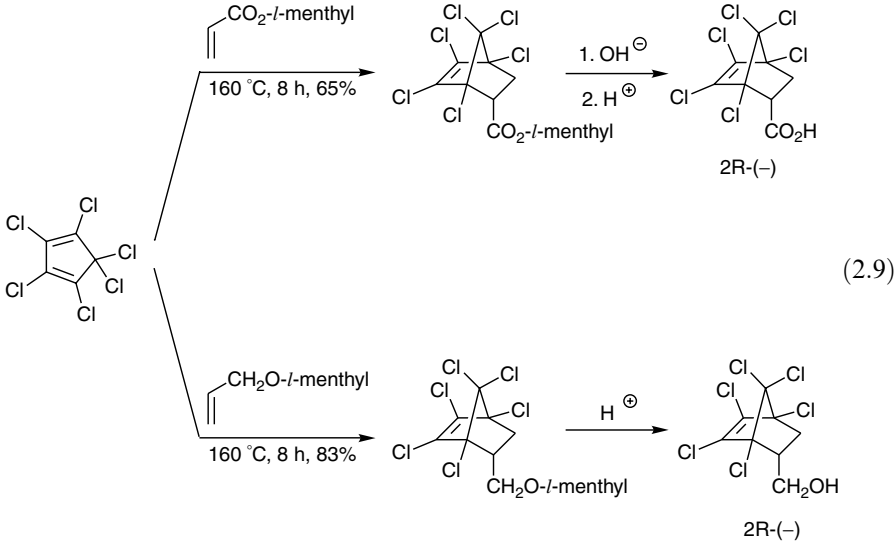
DropBooks

Scheme 2.12

Optically active norbornene derivatives [26] have been prepared by cycloaddition of hexachlorocyclopentadiene with *l*-menthylacrylate and *l*-menthylallylether (Equation 2.9). Low levels of enantiomeric excess have been obtained in the thermal processes, whereas Lewis acid catalyzed reactions (BF_3, BBr_3, $AlCl_3$, $SnCl_4$, DCM, 40–80 °C) gave better results.

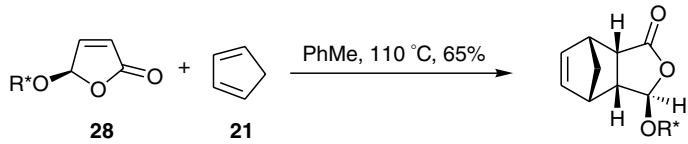


Scheme 2.13



(2.9)

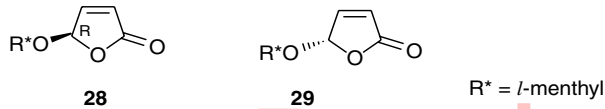
Furanones are a class of chiral dienophiles very reactive in thermal cycloadditions. For example, (5R)-5-(*l*-menthyloxy)-2-(5H)-furanone **(28)** underwent Diels–Alder reaction with cyclopentadiene **(21)** with complete π-face-selectivity (Equation 2.10), affording a cycloadduct which was used as a key intermediate in the synthesis of dehydro aspidospermidine [27].



28 **21** (2.10)

R* = *l*-menthyl

Very high levels of diastereomeric and enantiomeric excess have been observed in the cycloadditions of (5R) and (5S)-5-menthyloxy-2(5H)-furanones **28** and **29** (Figure 2.2), readily available from furfural and *d*- and *l*-menthol [28].



28 **29** R* = *l*-menthyl

Figure 2.2

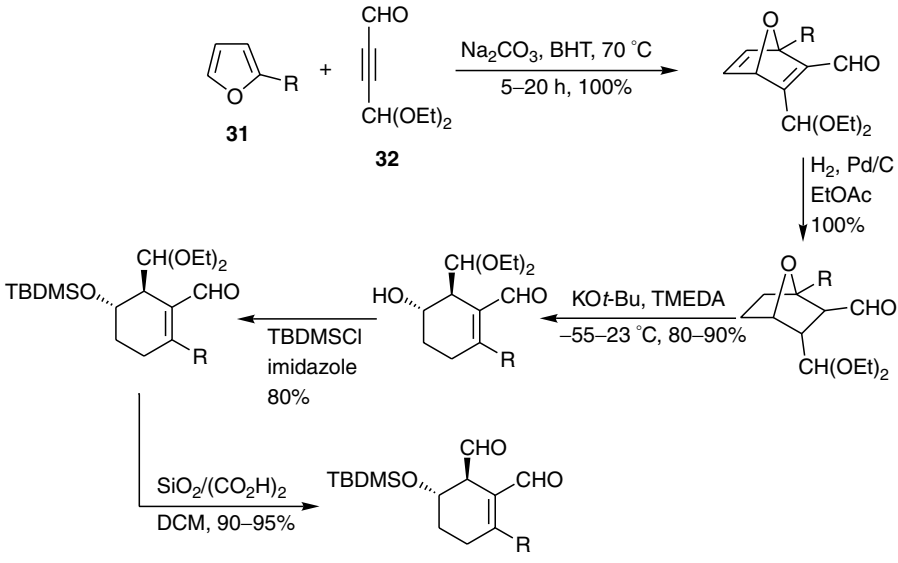
DropBooks

2.2.3 Heterocyclic Dienes

The reactivity of heterocyclic dienes is determined by the nature and number of heteroatoms and, in the case of heteroaromatic compounds, also by the aromatic character. Furans undergo Diels–Alder reactions with strong dienophiles and generally afford *exo*-cycloadducts which are thermodynamically more stable than the kinetically favoured *endo*-adducts.

An example of the Diels–Alder reaction of furans is the cycloaddition of **31** with 4,4-diethoxybut-2-ynal **(32)** which acts as an acetylenedicarbaldehyde synthon to afford 7-oxabicyclo [2.2.1]heptene derivatives [29] which were then converted into substituted cyclohex-1-ene-1,6-dicarbaldehydes by a four-step procedure (Scheme 2.14).

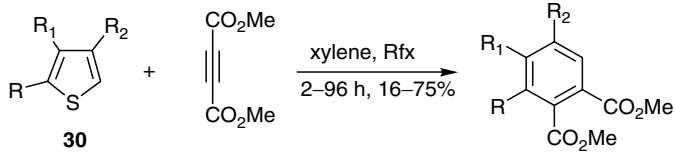
Thiophenes are less reactive than furans and therefore react with very reactive dienophiles. They behave somewhat differently from furans and in many cases the intermediate addition products are unstable and undergo cheleotropic extrusion of sulfur [30]. Thiophenes **30** undergo cycloaddition reactions with DMAD (Equation 2.11) to afford bicyclic cycloadducts which lead to phthalates by sulfur extrusion, thus offering a one-pot synthesis of dimethylphthalates [31].



R = Me, Et, Bu, *n*-C_5H_{11}, *n*-C_7H_{15}, *n*-C_8H_{17}

Scheme 2.14

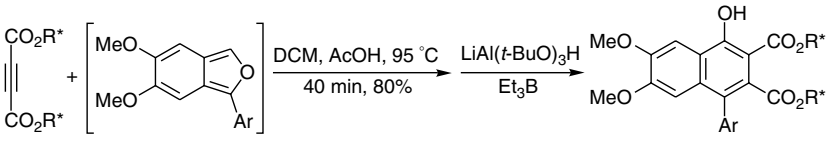
Benzo[c]furans (isobenzofurans) are very reactive but generally unstable dienes which are prepared *in situ* and trapped. The *in situ*-generated isobenzofuran **33** was trapped by cycloaddition reaction with bis(methyl (S)-lactyl) ester **34** to afford [32] optically active naphthols (Equation 2.12). The cycloaddition was carried out in the presence of a catalytic amount of glacial acetic acid and represents a facile one-pot procedure to synthesize substituted naphthols.



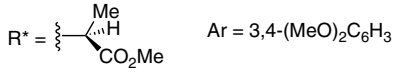
(2.11)

R, R_1, R_2 = H, Me, OMe, SMe, Ph

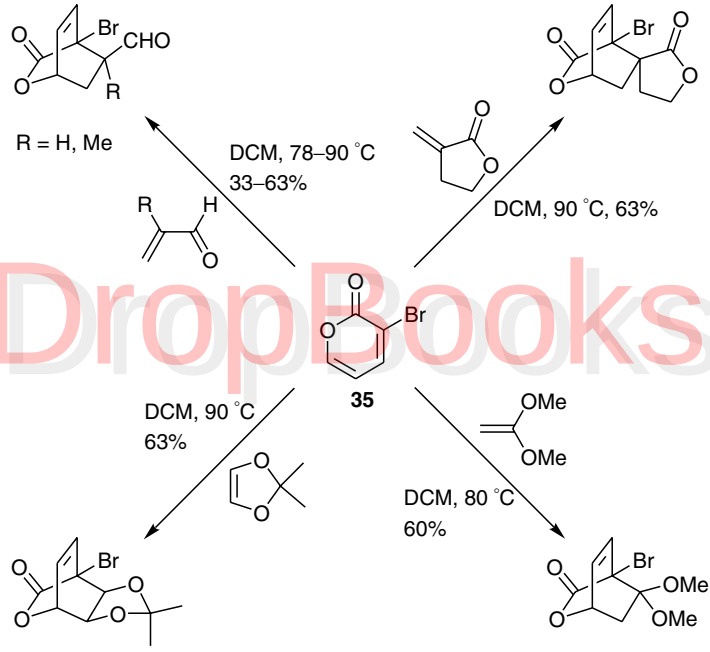
Because of their low reactivity, a Diels–Alder reaction of 2-pyrones usually requires such a high temperature that the initial bicyclic lactone adducts often undergo cycloreversion [30,33] with loss of CO_2. In some cases this limitation has been overcome by carrying out the reaction under high pressure conditions. Posner and coworkers have shown [34–36] that the presence of a tolylthio group or a bromine atom at the 3- or 5-position increases the reactivity of 2-pyrones. 3-Bromo-2-pyrone **(35)** (Scheme 2.15), as well as its regioisomer 5-bromo **(36)**



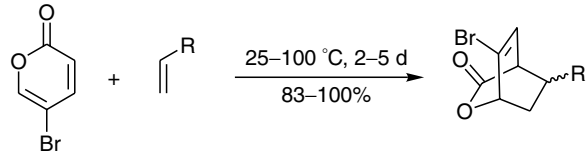
34 **33** (2.12)



(Equation 2.13), undergo slow but very clean regioselective cycloaddition reactions, under carefully controlled thermal conditions with both electron-poor and electron-rich dienophiles.



Scheme 2.15



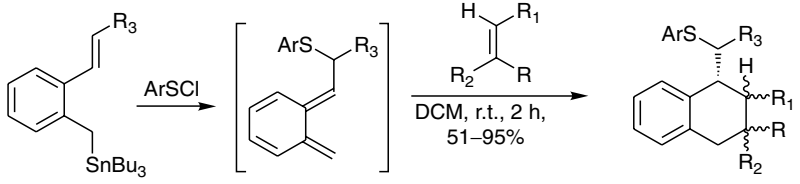
36 (2.13)

R = CN, COMe, CO_2H, OCH_2CH_2Cl, $OSiMePh_2$, *p*-Br-C_6H_4

2.2.4 Outer-Ring Dienes

Outer-ring dienes are very reactive and readily form Diels–Alder adducts with olefinic and acetylenic dienophiles. Several types of outer-ring dienes are based on their nature (carbodiene or heterodiene) and ring type (carbocyclic or heterocyclic). Their reactivity is related to the distance between the methylene carbons and is strongly influenced by the presence of heteroatoms in the ring and substituents in the diene moiety. Many routes for generating these dienes from precursors have been studied; when generated in the presence of a dienophile, they give the adducts directly [30].

Various *o*-quinodimethanes, generated *in situ* from *o*-alkenylbenzyltributylstannane precursors, have been used to synthesize functionalized polycycles by Diels–Alder reaction with maleic anhydride, methylacrylate, dimethylfumarate and N-phenyl maleimide in the presence of electrophiles [37] (Scheme 2.16).



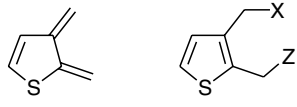
R-R$_1$= —C(=O)—O—C(=O)—, R$_2$ = H; R = CO_2Me, R$_1$ = R$_2$ = H

R$_1$ = R$_2$ = CO_2Me, R = H; R-R$_1$ = —C(=O)—N(Ph)—C(=O)—, R$_2$ = H

Ar = Ph, *o*-$NO_2C_6H_4$; R$_3$ = H, Me, Ph, CO_2Et

Scheme 2.16

2,3-Dimethylene-2,3-dihydrothiophene (**37**, Figure 2.3) is the thiophene analog [38] of *o*-quinodimethanes and has been used to develop a Diels–Alder-based synthetic approach to benzothiophene derivatives. Generated *in situ* by treating the trimethylsylyl ammonium derivatives **38** or **39** with $Bu_4N^+F^-$, it



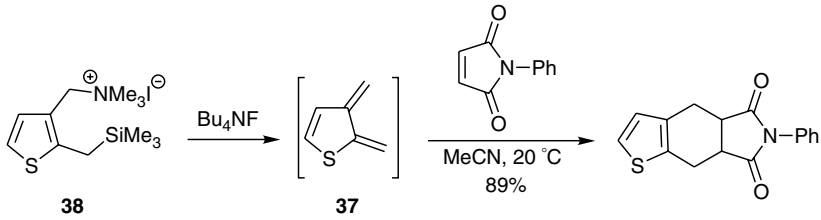
37

38 X = $Me_3N^+I^-$; Z = $SiMe_3$

39 X = $SiMe_3$; Z = $MeEt_2N^+I^-$

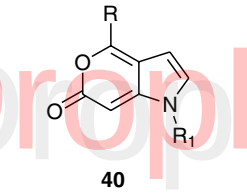
Figure 2.3

has been trapped with a variety of dienophiles (dimethyl maleate and fumarate, acrylonitrile, methylacrylate, diethylazodicarboxylate). The fluoride-induced 1,4-elimination procedure [39] allows **37** to be generated under mild conditions; this is of particular importance due to the strong tendency of diene **37** to dimerize or polymerize. For example, the reaction of diene **37** with N-phenyl maleimide is described in Equation 2.14.



38 **37** (2.14)

Pyrano-[4,2-b]-pyrrol-5-ones **(40)** and pyrano-[4,3-b]-pyrrol-6-ones **(41)** (Figure 2.4) are stable cyclic analogs of pyrrole 2,3-quinodimethane and undergo Diels–Alder reaction [40, 41] with various dienophiles to afford indole derivatives after loss of carbon dioxide.



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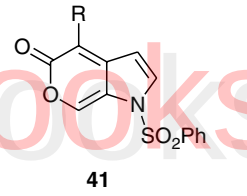

41

R = H, Me; $R_1 = CO_2$*i*-Bu

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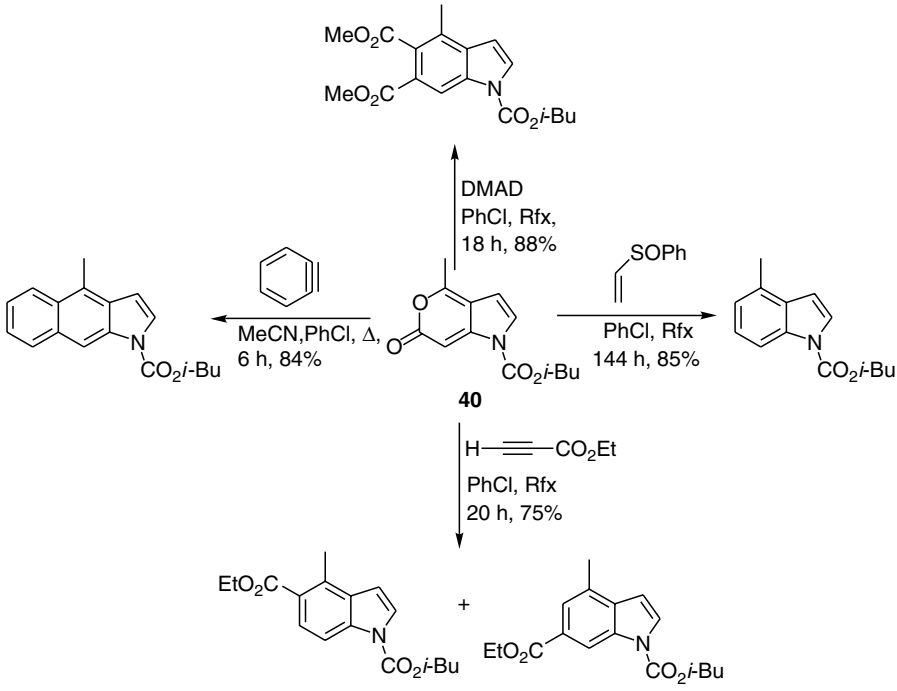
Figure 2.4

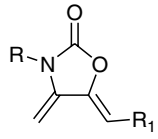
Scheme 2.17 reports some cycloaddition reactions of pyrano-[4,3-b]-pyrrole **40** (R = Me, $R_1 = CO_2$-*i*-Bu).

Tamariz and coworkers [42] have described a versatile, efficient methodology for preparing N-substituted-4,5-dimethylene-2-oxazolidinones **42** (Figure 2.5) from α-diketones and isocyanates and have also studied their reactivity in Diels–Alder reactions. This is a method for synthesizing polycyclic heterocyclic compounds. Some of the reactions of diene **42** are summarized in Scheme 2.18. The nitrogen atom seems to control the regiochemistry of the reaction.

2,3-Ethylene disulfonyl-1,3-butadiene **(43)** is an example of an outer-ring diene with a non-aromatic six-membered heterocyclic ring containing sulfur. It is prepared by thermolysis of sulfolenes in the presence of a basic catalyst. It is very reactive [43] and even though it is electron-deficient, it readily reacted with both electron-rich and electron-poor dienophiles (Equation 2.15).



Scheme 2.17



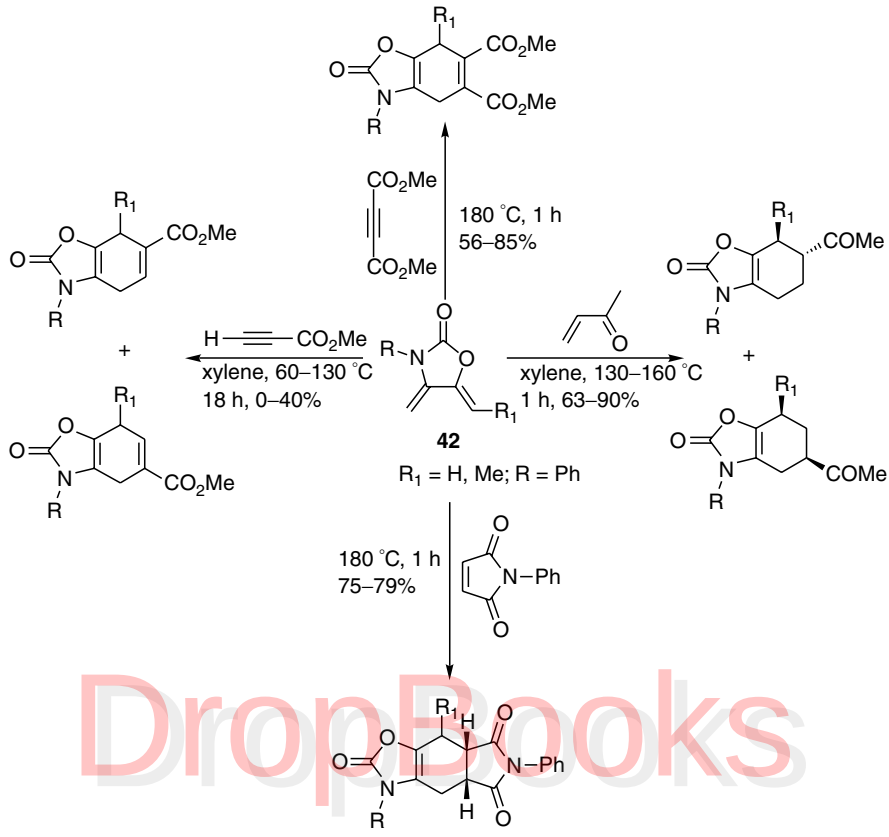
42

R = $(CH_2)_2Cl$, Ph, *p*-ClC_6H_4, *m*-ClC_6H_4, *o*-MeC_6H_4, *m*-MeC_6H_4, *p*-MeC_6H_4, *o*-BrC_6H_4
R_1 = H, Me

Figure 2.5

Indole-2,3-quinodimethanes [44] **44** are bicyclic outer-ring dienes that are widely used to prepare a variety of heterocyclic polycyclic compounds. These dienes, generated by extrusion of CO_2 from lactones, are then trapped by dienophiles. Some examples of Diels–Alder reactions of the dienes **44** are reported in Scheme 2.19.

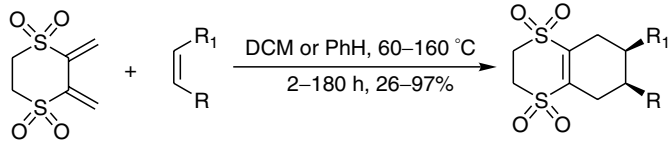
The Diels–Alder reaction provides a valuable tool for functionalizing buckminsterfullerene (C_{60}). Functionalized C_{60} derivatives may have important applications as conductive materials [45] and in biological chemistry [46].



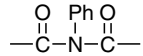
Scheme 2.18

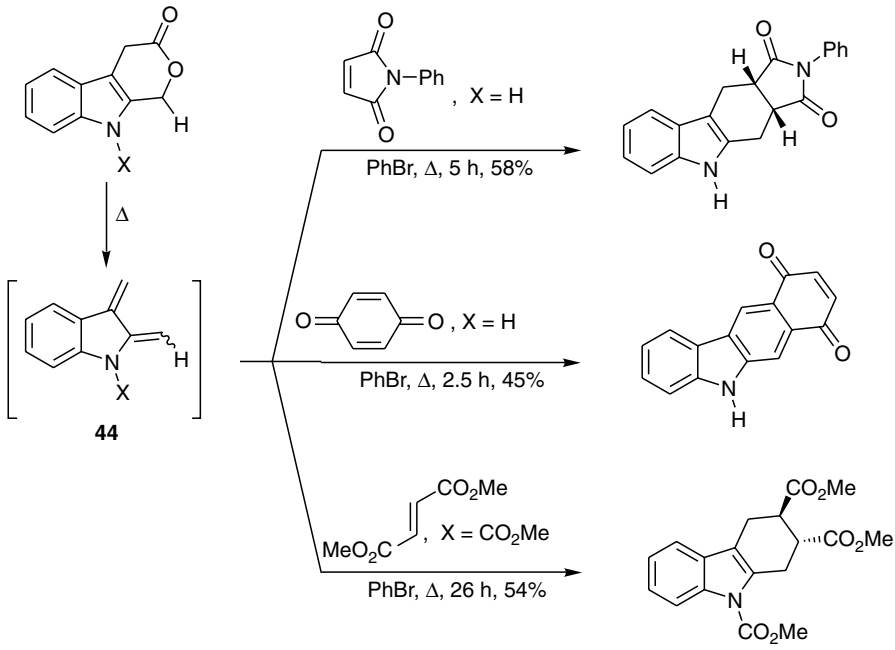
o-Quinodimethanes and their heterocyclic analogs have been used to functionalize (C_{60}) fullerene by cycloaddition reactions affording thermally stabilized cycloadducts.

Thieno-*o*-quinodimethanes **46** and **48**, generated *in situ* by iodide-induced 1,4-elimination from the respective 2,3-bis(chloromethyl)thiophene **45** and 2,3-bis(bromomethyl)benzo[b]thiophene **47** precursors, undergo Diels–Alder



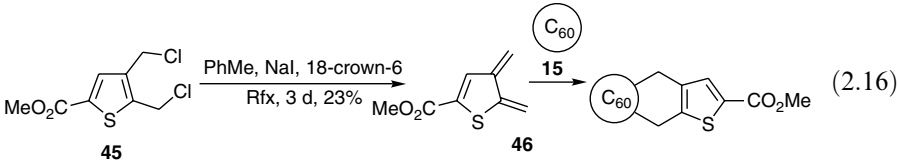
43 (2.15)

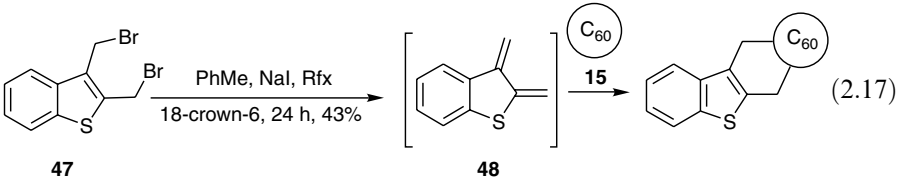
R = OEt, SPh, TMS, OAc, CO_2Me, COMe, Ph; R_1 = H; R-R_1 = $-(CH_2)_4-$, 



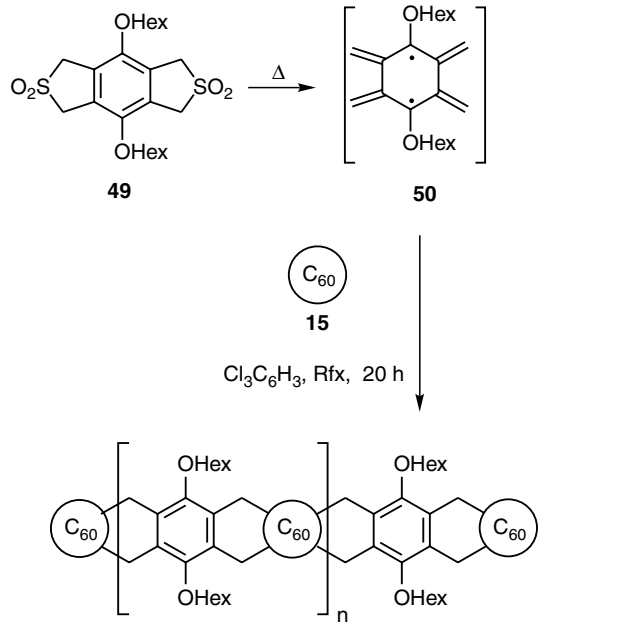
Scheme 2.19

reaction with fullerene **(15)** in the presence of 18-crown-6 ether, yielding (Equations 2.16 and 2.17) thiophene-containing monocycloadducts [47].





Bis-*o*-quinodimethanes have also been used to functionalize [60]-fullerene by Diels–Alder reaction. An example is the preparation of main-chain polymers with incorporated [60]-fullerene units [48] illustrated in Scheme 2.20. Cycloaddition of bis-diene **50** generated *in situ* from bis-sulfone **49** with [60]-fullerene leads to an oligomer mixture **51**. Another type of functionalization is based on the



Scheme 2.20

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Diels–Alder reaction of fullerenes with complex dienes type **52** (Figure 2.6) which have a 2,3-bis-(methylene) bicyclo[2.2.2]octane unit [49].

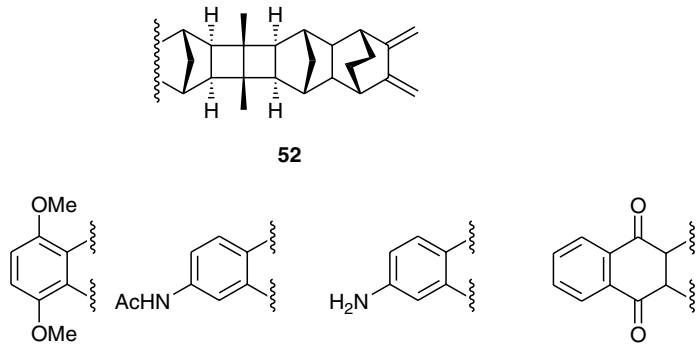
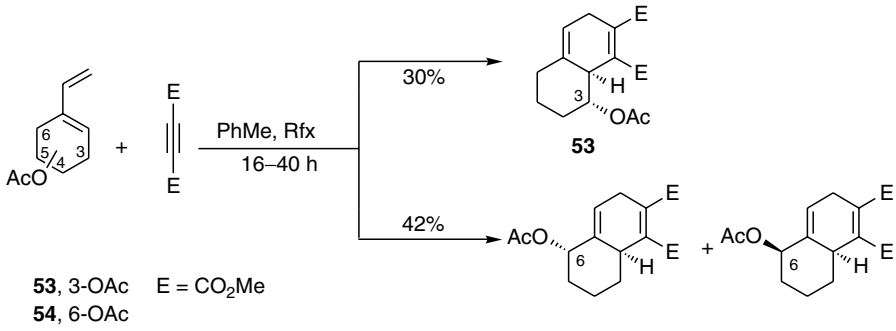


Figure 2.6

2.2.5 Inner-Outer-Ring Dienes

Inner-outer-ring dienes are very useful in the synthesis of polycyclic molecules. Their reactivity in the Diels–Alder reaction depends on the type of ring (carbocyclic, heterocyclic, aromatic) that bears the ethenyl group or on the electronic effects of substituents at the diene moiety [30].

The 3- and 6-acetoxyvinylcyclohexenes **53** and **54** react with dimethylacetylenedicarboxylate to afford bicyclic esters [50]. It is noteworthy that the facial diastereoselectivity depends on the position of the acetoxy group (Scheme 2.21). While the reaction of **53** is completely *anti*-diastereoselective, that of **54** is undiastereoselective, affording a 1:1 mixture of cycloadducts.

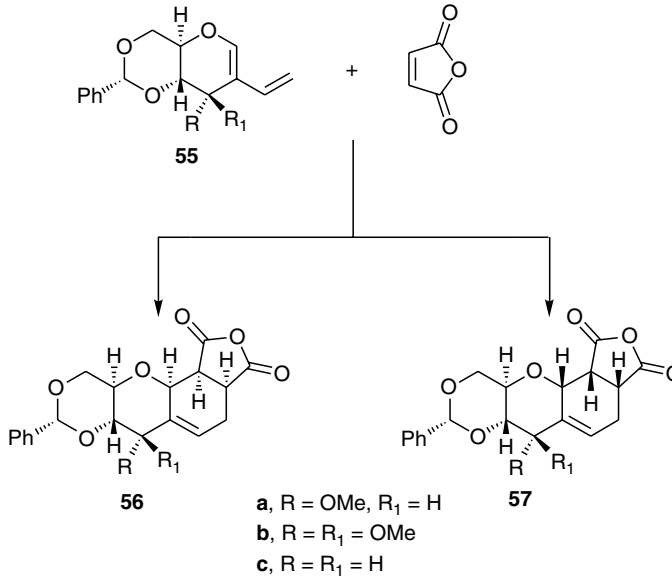


Scheme 2.21

The cycloadditions of the C-2 vinyl glicals with maleic anhydride are an interesting example of facial stereocontrol. The allylic methoxy group in dienes **55a** and **55b** exerts an *anti*-stereodirecting effect as shown by the stereochemistry of the *endo*-cycloadducts **56** and **57** obtained as the sole products from **55a** and **55b**, respectively, and by the fact that **55c** produces [51] a mixture of the diastereoisomers **56c** and **57c** (Scheme 2.22). When linear acetylenic dienophiles were used, the degree of facial diastereoselectivity decreased, which indicates its dependence on steric effects.

Styrenes and vinylnaphthalenes

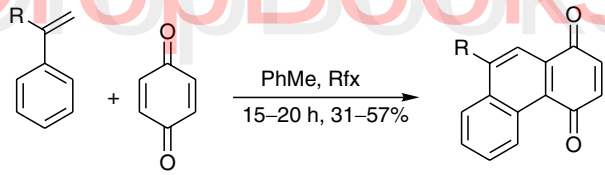
Styrenes may act as 2π and 4π components of the Diels–Alder reaction depending on the substitution site and the electronic effects of the substituent. Electron-donating groups at the α-carbon of the olefinic double bond enhance the dienic reactivity of styrenes [30].



Scheme 2.22

Phenanthrene-1,4-diones have been prepared [52] by cycloaddition of α-substituted styrenes with an excess of 1,4-benzoquinone (Equation 2.18). Initial cycloadducts are oxidized by 1,4-benzoquinone.

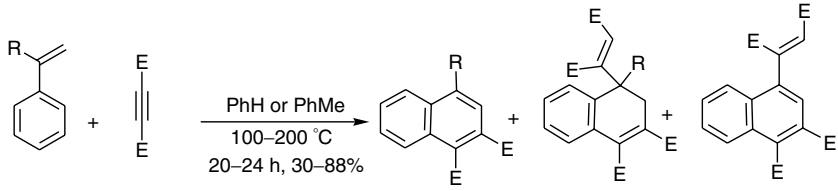
DropBooks



(2.18)

R = H, OMe, SMe, $Me(CH_2)_3O(CH_2)_2O$

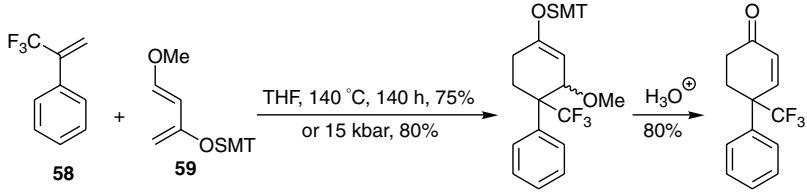
In contrast, product mixtures were obtained [53] when α-substituted styrenes were reacted with dimethylacetylenedicarboxylate (Equation 2.19). The products were formed via aromatization of the primary cycloadducts or by '*ene*' addition of a second molecule of DMAD.



(2.19)

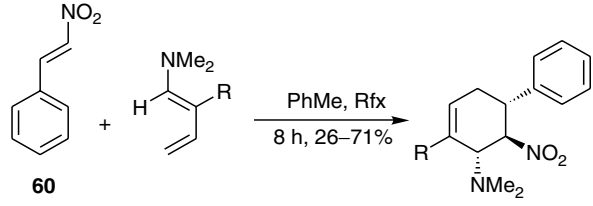
R = OMe, OEt, $OSiMe_3$; E = CO_2Me

When strong electron-withdrawing substituents were introduced at the α- or β-carbon of the vinyl group, the styrenes acted as dienophiles. Thus cycloaddition of α-trifluoromethyl styrene **(58)** with Danishefsky's diene **59** afforded regioselectively a 1:1 mixture of cycloadducts which were then converted (Equation 2.20) into 4-phenyl-4-trifluoromethyl-2-cyclohexen-1-one [54].



(2.20)

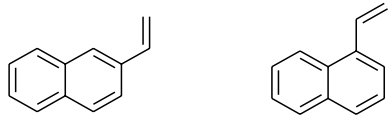
Similarly, β-nitrostyrene **(60)** reacted with 1-dimethylamino-1-alkylbutadienes to afford phenylnitrocyclohexenes [55] (Equation 2.21) regioselectively and stereoselectively.



(2.21)

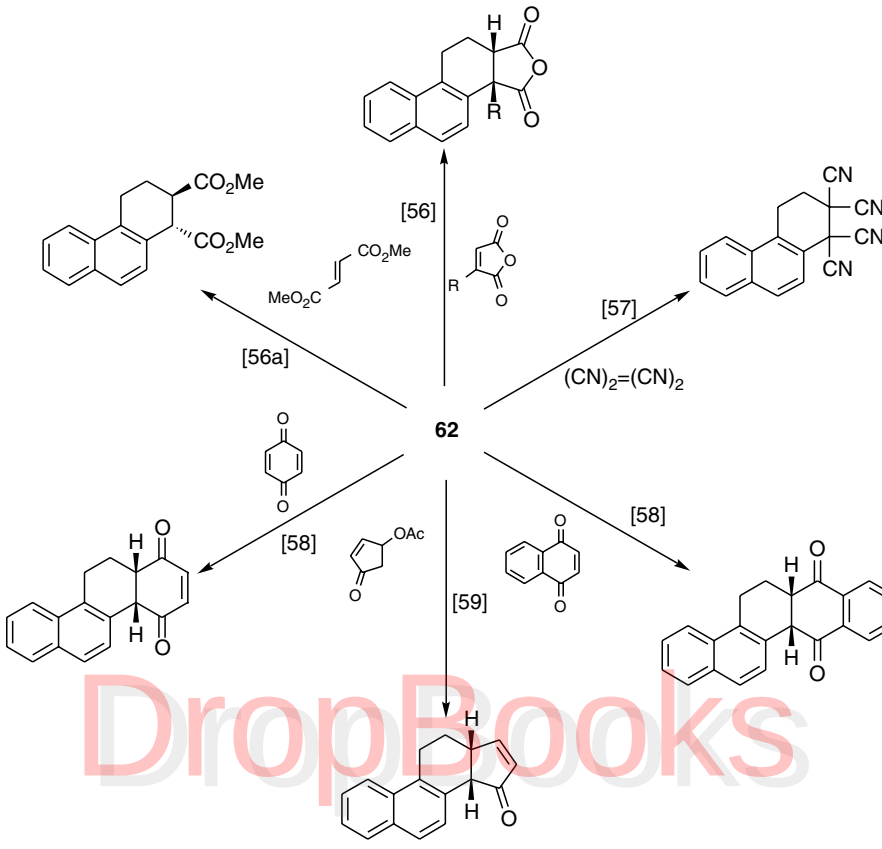
R = Me, Et, *i*-Pr, *n*-Pr, *n*-Bu

1-Vinylnaphthalenes give Diels–Alder reactions more easily than styrenes and have been used to synthesize steroid-like compounds. 2-Vinylnaphthalene **(61)** is less reactive than 1-vinylnaphthalene **(62)** (Figure 2.7); it requires drastic conditions to undergo Diels–Alder reaction and the yields are low. Better results can be obtained by carrying out the reaction under high pressure (Chapter 5). Some Diels–Alder reactions of 1-vinylnaphthalene **(62)** are summarized in Scheme 2.23.



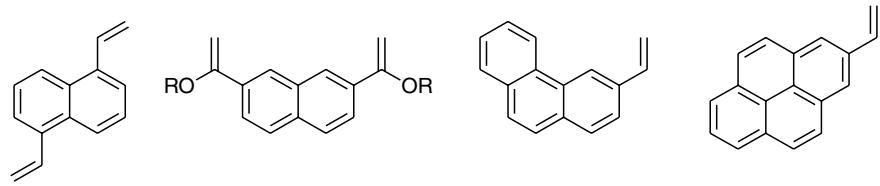
61 **62**

Figure 2.7



Scheme 2.23

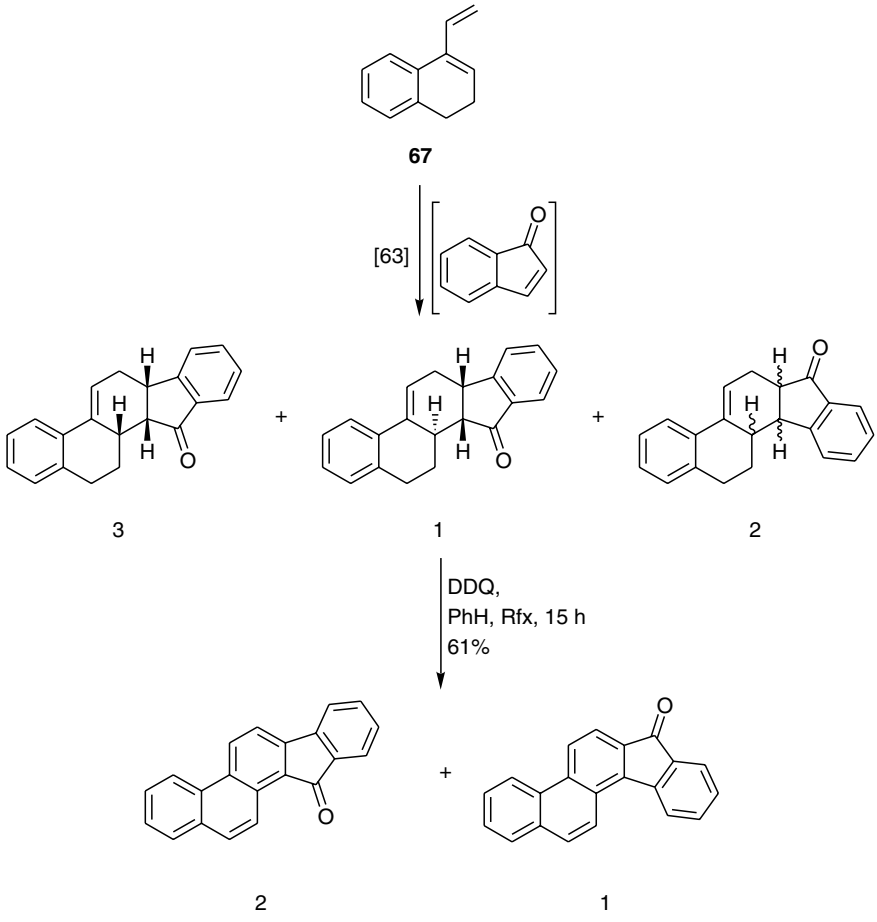
Divinylnaphthalenes **63** and **64** (Figure 2.8) react with strong dienophiles and have been used to synthesize complex polycyclic aromatic compounds [60]. While 2-vinylnaphthalene **(61)** and 1-vinylnaphthalene **(62)** act as 4π components, 3-vinylphenanthrene **(65)** and 1- vinylpyrene **(66)** (Figure 2.8), characterized by an extended polycyclic aromatic system, preferentially undergo [2+2] cycloaddition [57, 61, 62].



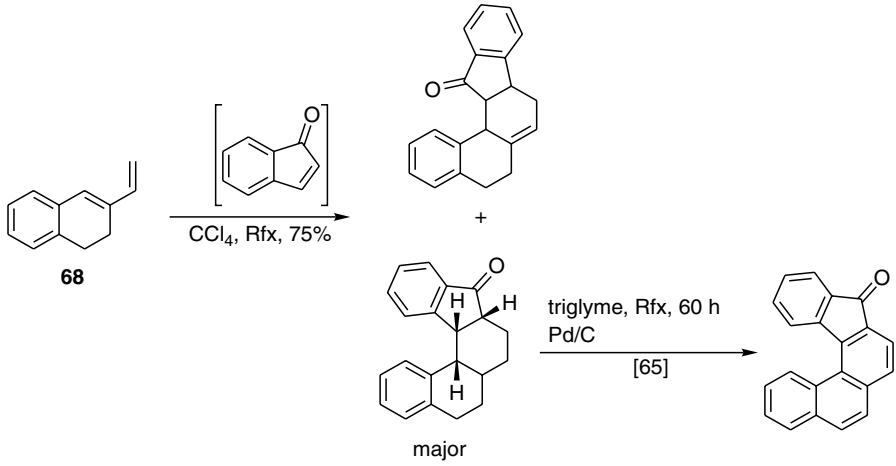
63 **64** **65** **66**

Figure 2.8

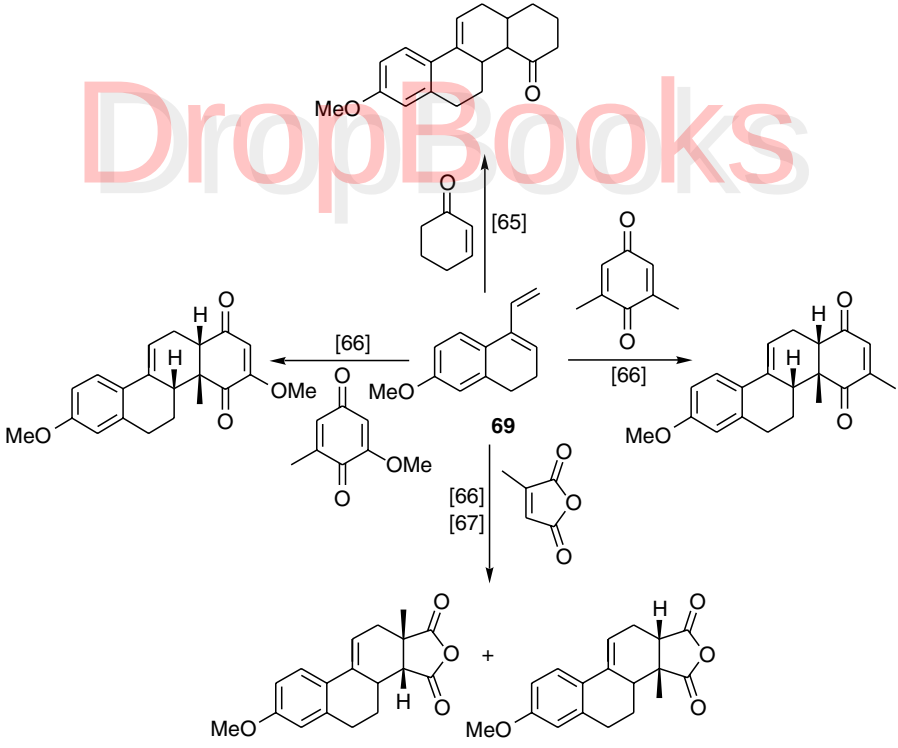
3,4-Dihydro-1-vinylnaphthalene **(67)** as well as 3,4-dihydro-2-vinylnaphthalene **(68)** are more reactive than the corresponding aromatic dienes. Therefore they may also undergo cycloaddition reactions with low reactive dienophiles, thus showing a wider range of applications in organic synthesis. The cycloadditions of dienes **67** and **68** and of the 6-methoxy-2,4-dihydro-1-vinylnaphthalene **69** have been used extensively in the synthesis of steroids, heterocyclic compounds and polycyclic aromatic compounds. Some of the reactions of dienes **67–69** are summarized in Schemes 2.24, 2.25 and 2.26. In order to synthesize indeno[c]phenanthrenones, the cycloaddition of diene **67** with 3-bromoindan-1-one, which is a precursor of inden-1-one, was studied. Bromoindanone was prepared by treating commercially available indanone with NBS [64].



Scheme 2.24



Scheme 2.25

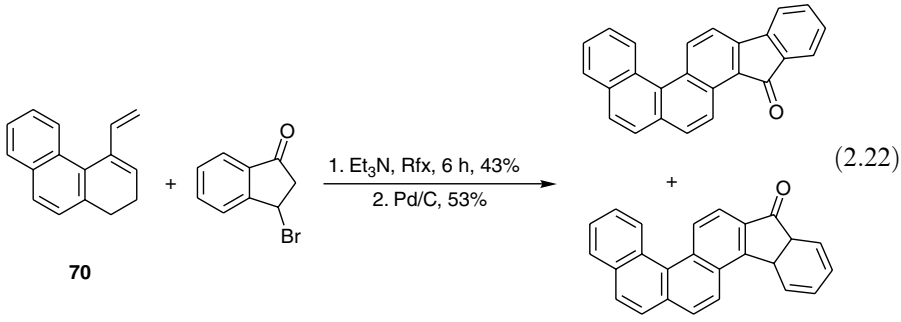


Scheme 2.26

DropBooks

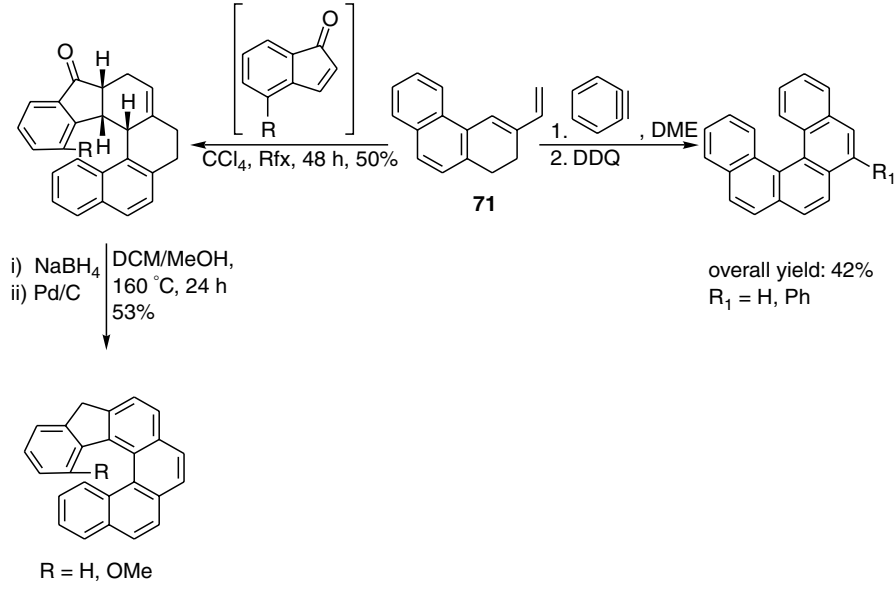
Dihydrovinylphenanthrenes

Dihydrovinylphenanthrenes are more reactive than the corresponding vinyl phenanthrenes and undergo Diels–Alder reactions easily. They have been used in the synthesis of polycyclic aromatic compounds and helicenes. Examples of cycloaddition reactions of the 3,4-dihydro-1-vinylphenanthrene **(70)**, [61] 3,4-dihydro-2-vinylphenanthrene **(71)** [68] and 1,2-dihydro-4-vinylphenanthrene **(72)** [69] are reported in Equation 2.22 and Schemes 2.27 and 2.28.

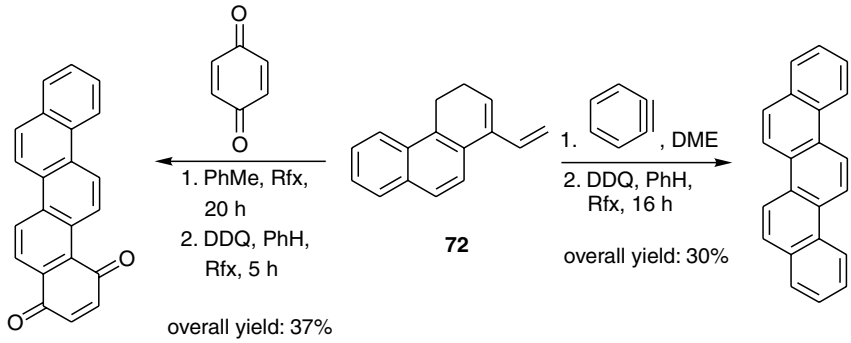


70 (2.22)

In the case of the cycloaddition of **71** with benzyne (Scheme 2.27) a 1.5:1 mixture of the two products was obtained which were then oxidized to the



Scheme 2.27



Scheme 2.28

corresponding aromatic compounds. The major component was the product of the cycloaddition which originated the minor product by *ene*-reaction with a second molecule of dienophile.

The Diels–Alder reactions of **71** with 2-inden-1-ones generated *in situ* by treating the corresponding 3-bromo-indan-1-ones with triethylamine, were highly regio- and stereoselective; the cycloadducts were easily dehydrogenated to afford helicenes. Diene **72** underwent cycloaddition reactions with p-benzoquinone and benzyne to give cycloadducts which were dehydrogenated to [5]-phenacenes.

DropBooks

Vinylfurans, vinylthiophenes and vinylpyrroles

2-Vinylfuran **(73a)** and 2-vinylthiophene **(73b)** (Figure 2.9), and more generally 2-vinyl- and 3-vinyl five-membered aromatic heterocycles and their benzoderivatives, may undergo Diels–Alder reaction in two different ways by involving either the aromatic nucleus (intra-annular addition) or the diene moiety including the side-chain double bond (extra-annular addition). The latter way of interacting is preferred [30] and involves mechanistic and theoretical aspects, allowing substituted condensed heterocyclic systems to be synthesized [70].

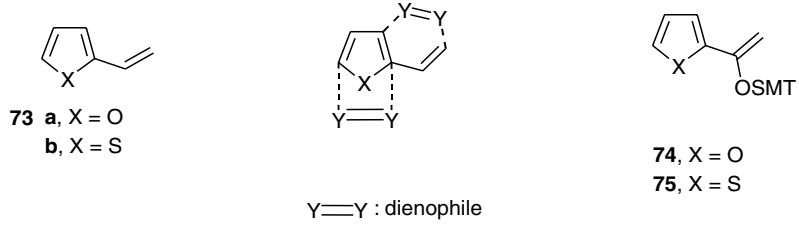
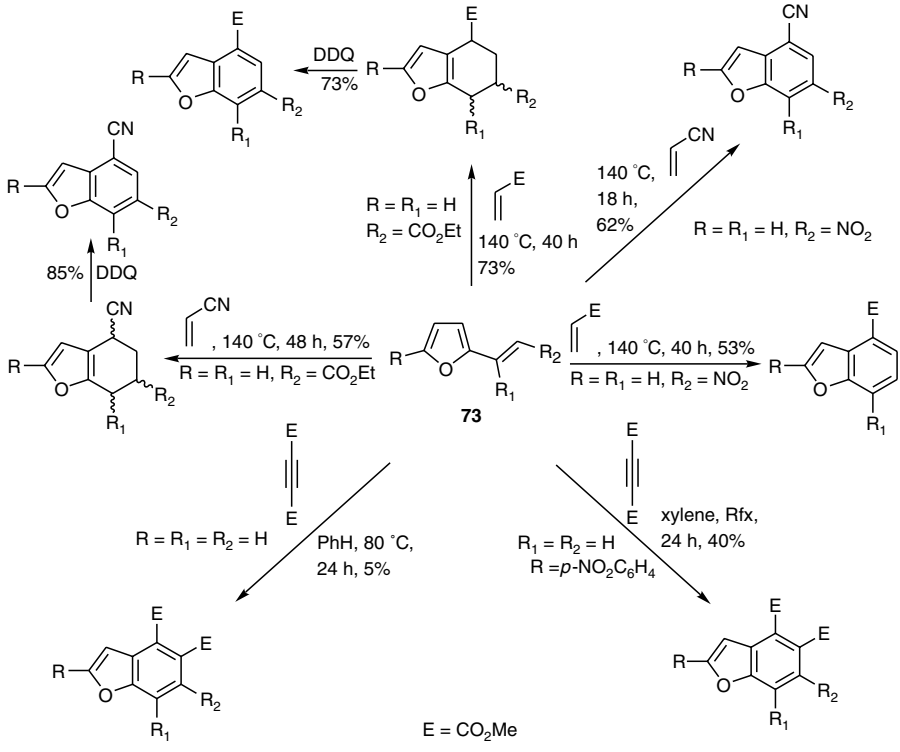


Figure 2.9

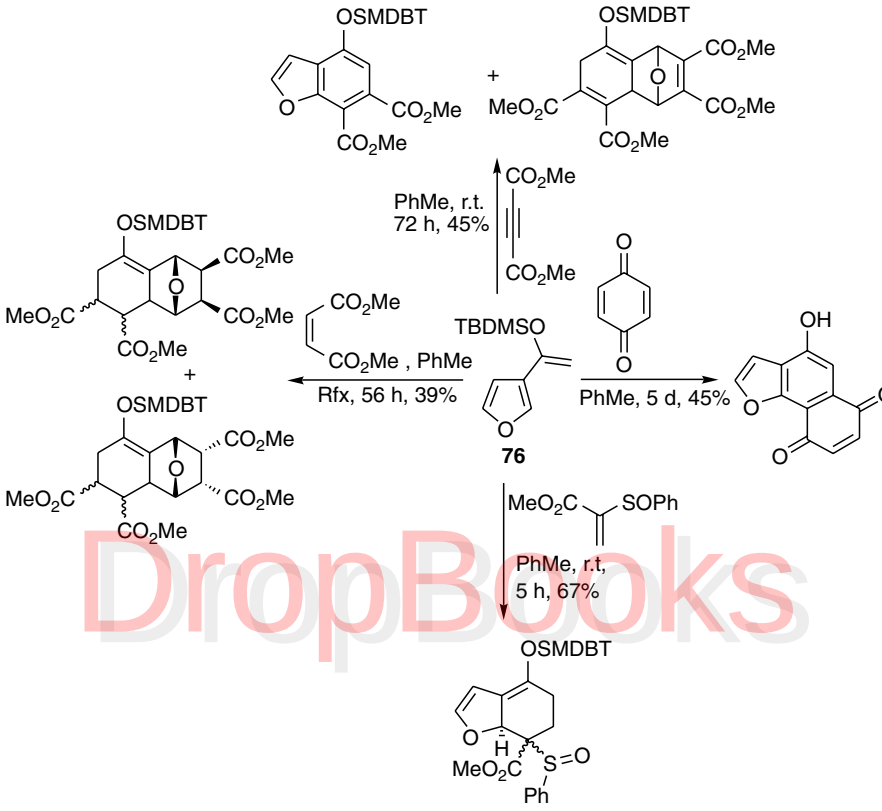
Whereas furan is more reactive than thiophene, according to the different aromatic character [71], the corresponding vinyltrimethylsilyloxy derivatives **74** and **75** show an opposite order of reactivity [72]. The reversed reactivity has been explained in terms of FMO theory by considering the higher energy of the HOMO (diene) and the larger HOMO coefficient at the end of the silyloxyvinyl group in the thiophene derivative **75** compared with that in the analogous furan **74**. This shows that the reactivity of vinylheterocycles is not simply related to their aromaticity.

The Diels–Alder reaction of 2-vinylfurans **73** with suitable dienophiles has been used to prepare tetrahydrobenzofurans [73, 74] by an extra-annular addition; these are useful precursors of substituted benzofurans (Scheme 2.29). In practice, the cycloadditions with acetylenic dienophiles give fully aromatic benzofurans directly, because the intermediate cycloadducts autoxidize during the reaction or in the isolation procedure. In the case of a reaction with nitro-substituted vinylbenzofuran, the formation of the aromatic products involves the loss of HNO_2.



Scheme 2.29

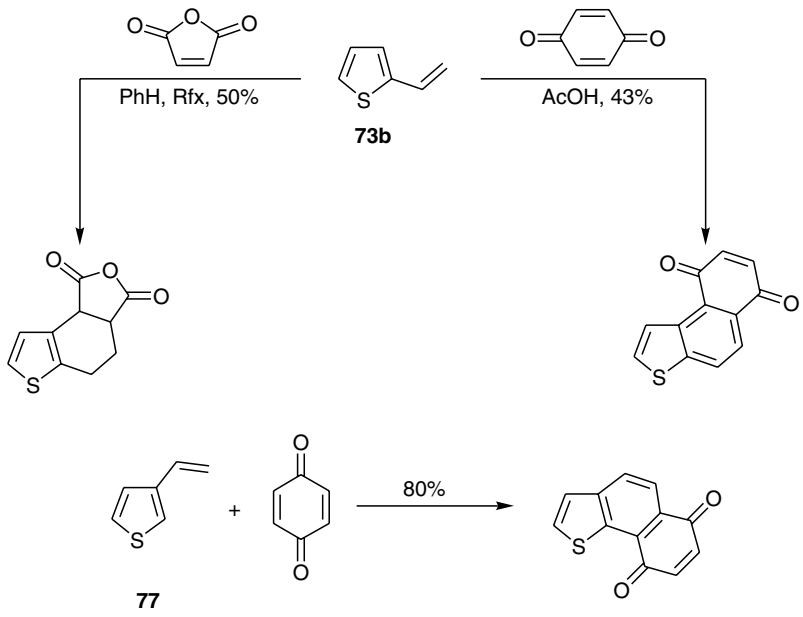
There is marked competition between intra-annulation and extra-annular addition in the case of 3-vinylfuran as shown by the results of the cycloaddition of **76** with several dienophiles [75] (Scheme 2.30).



Scheme 2.30

2-Vinyl- and 3-vinylthiophene (**73b** and **77**) are less reactive than the corresponding furans and show a notable preference for extra-annular addition due to the higher reactivity of the diene system, including the side-chain double bond. 2-Vinylthiophene is less reactive than 3-vinylthiophene. Whereas 2-vinylthiophene **(73b)** reacted with maleic anhydride and 1,4-benzoquinone to give cycloadducts in reasonable yield, 3-vinylthiophene **(77)** gave a higher yield of the cycloadduct [76, 77] (Scheme 2.31).

Vinylpyrazoles fail to undergo cycloaddition reactions under conditions used for vinylfurans and vinylthiophenes. 1-Phenyl-4-vinylpyrazole **(78)** and 1-phenyl-5-vinylpyrazole **(79)** (Figure 2.10) react only with strong dienophiles under pressure and at high temperatures [78–80].



Scheme 2.31

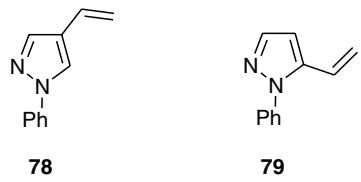
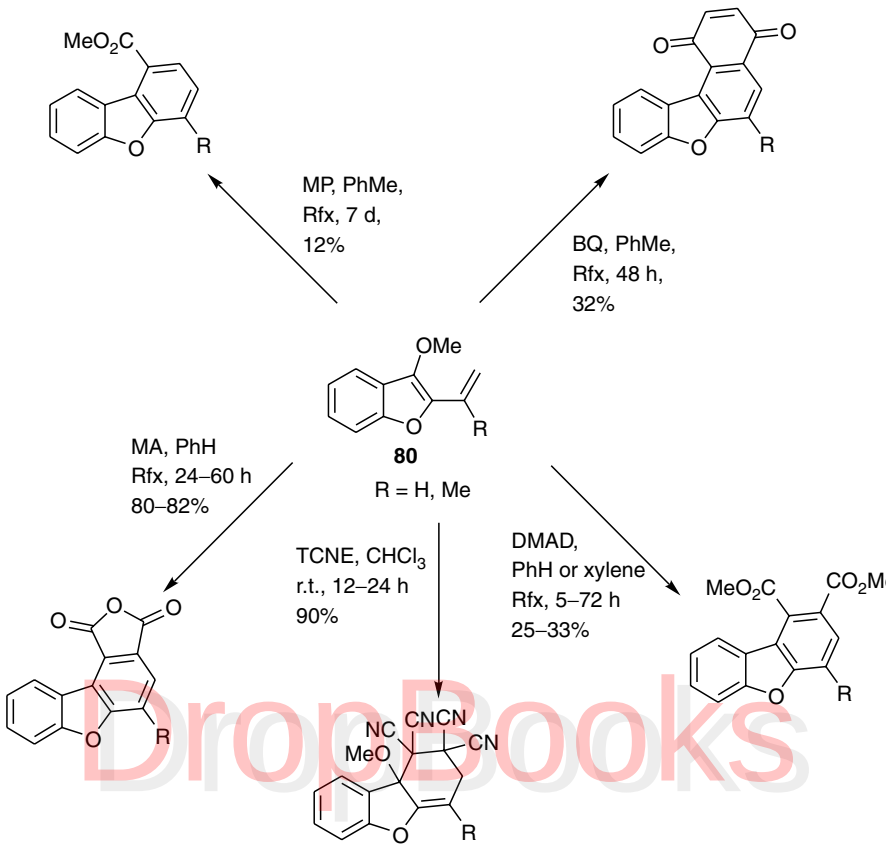


Figure 2.10

Vinylbenzofurans, vinylbenzothiophenes and vinylindoles

These dienes are valuable for the Diels–Alder based synthesis of dibenzofurans, dibenzothiophenes, carbazoles and other classes of complex polycyclic heterocyclic compounds. Scheme 2.32 summarizes some of the cycloadditions [81] of 2-vinylbenzofurans **(80)**.

Substituted dibenzofurans have also been obtained by cycloaddition of 3-vinylbenzofurans **(81)** as shown [82] in Scheme 2.33.



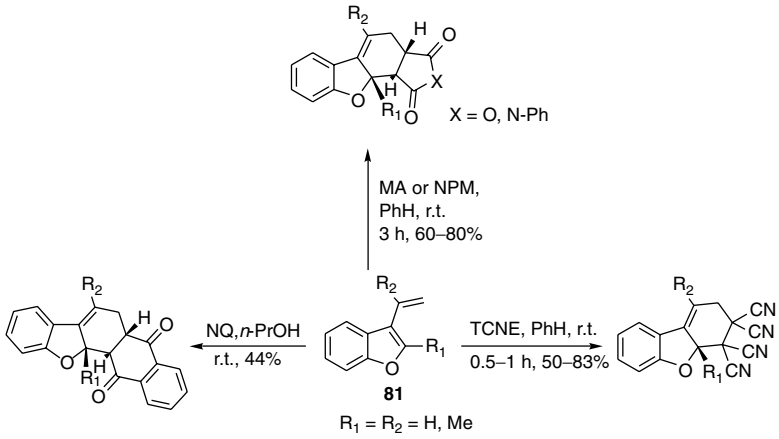
MP = methylpropiolate; BQ = 1,4-benzoquinone; MA = maleic anhydride;
DMAD = dimethylacetylenedicarboxylate; TCNE = tetracyanoethylene

Scheme 2.32

As vinylbenzofurans allow a large variety of substituted dibenzofurans to be synthesized, 2- and 3-vinylbenzo[b]thiophenes allow an easy entry, by Diels–Alder reaction with the appropriate dienophiles, to substituted dibenzothiophenes which are not easily accessible by other methods. Vinylbenzo[b]thiophenes are less reactive than the corresponding vinylbenzo[b]furans. Some cycloaddition reactions of 2-vinylbenzo[b]thiophene **(82)** with various dienophiles are reported [83] in Scheme 2.34.

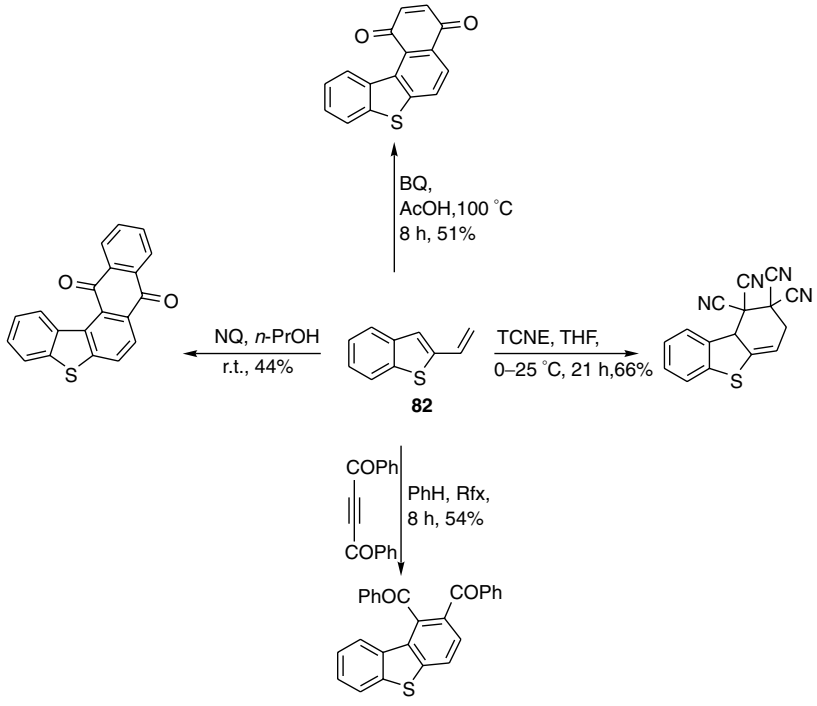
The Diels–Alder cycloadditions of both 2-vinylindoles and 3-vinylindoles are very attractive methods for preparing [b]annelated indoles to serve as lead substances and as building blocks for alkaloids. Pindur and coworkers [84] have extensively studied the vinylindole Diels–Alder chemistry.

Cycloaddition reactions of 2-vinylindoles **83** with a variety of dienophiles provide a convenient access [85] to carbazoles (Scheme 2.35).



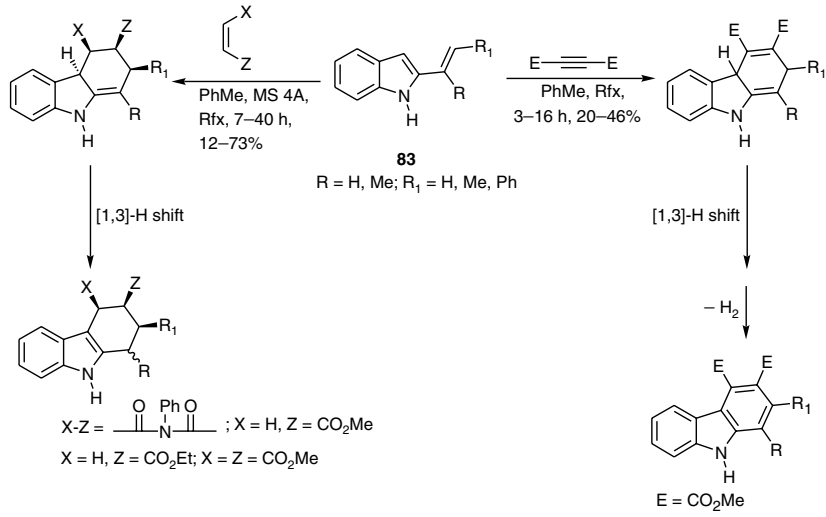
MA = maleic anhydride; NPM = N-phenylmaleimide; NQ = 1,4-naphthoquinone; TCNE = tetracyanoethylene

Scheme 2.33



BQ = 1,4-benzoquinone; NQ = 1,4-naphthoquinone; TCNE = tetracyanoethylene

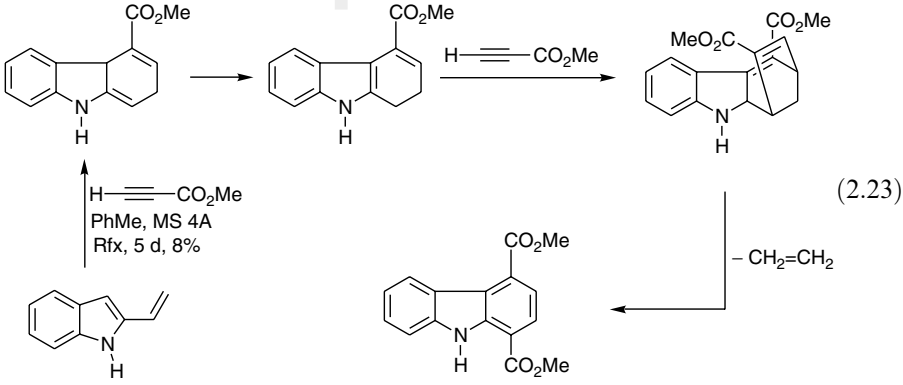
Scheme 2.34



Scheme 2.35

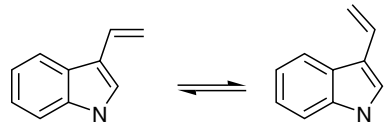
The reactivity and regioselectivity of the cycloadditions of the 2-vinylindoles are markedly dependent on the substitution pattern as shown by the calculated HOMO energies and coefficients [85a].

In the case of the reaction of 2-vinylindole (**83**, $R = R_1 = H$) with methyl propynoate, a diester is obtained by a multiple one-pot process involving two molecules of the dienophile and the extrusion of ethene (Equation 2.23).



(2.23)

3-Vinylindoles have been studied extensively and used in the synthesis of carbazoles, alkaloids and other classes of pharmacologically active compounds. MMX force field calculations have shown that coplanar *s-cis* and *s-trans* conformations of 3-vinylindole (**84**, Figure 2.11) are the most stable conformers; they exhibit only slight differences in their thermodynamic stabilities [86].

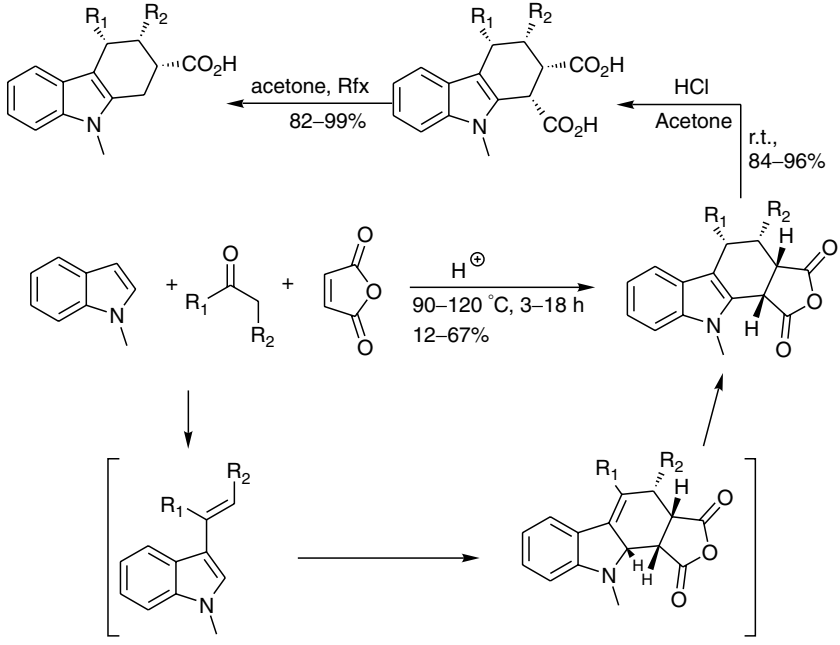


84

Figure 2.11

Preparation of 3-vinylindole **(84)** via Cope elimination of N,N-diethyltryptamine-N-oxide has been reported [87]. An alternate approach based on the Wittig reaction of the readily accessible N-phenylsulfonylindole-3-carbaldehyde failed because cleavage of the sulfonyl protecting group easily produced an anion whose neutralization led to polymerization [86].

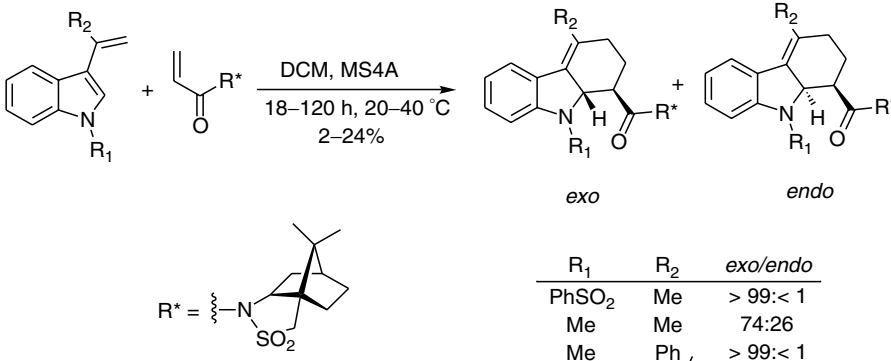
Noland and coworkers have developed an interesting methodology for the *in situ* synthesis of carbazoles. This methodology combines the synthesis of 3-vinylindoles from indoles and acyclic ketones with the subsequent Diels–Alder cycloaddition in one flask to produce a variety of tetrahydrocarbazoles [88] (Scheme 2.36).



R_1 = Me, Et, Ph, CH_2COMe, *p*- and *m*-XC_6H_4 (X = Me, OMe, Br, Cl, F, NO, Ph)
R_2 = H, Me, Et, Bn, Me_3CCOCH_2

Scheme 2.36

Enantiomerically pure tetrahydrocarbazoles have been obtained by asymmetric Diels–Alder reactions [89] of 2- vinyl- and 3-vinylindoles with Oppolzer's acryloylsultam. The results of the [4+2] cycloadditions of 3-vinylindoles (Scheme 2.37) show that the *exo*-addition is preferred.



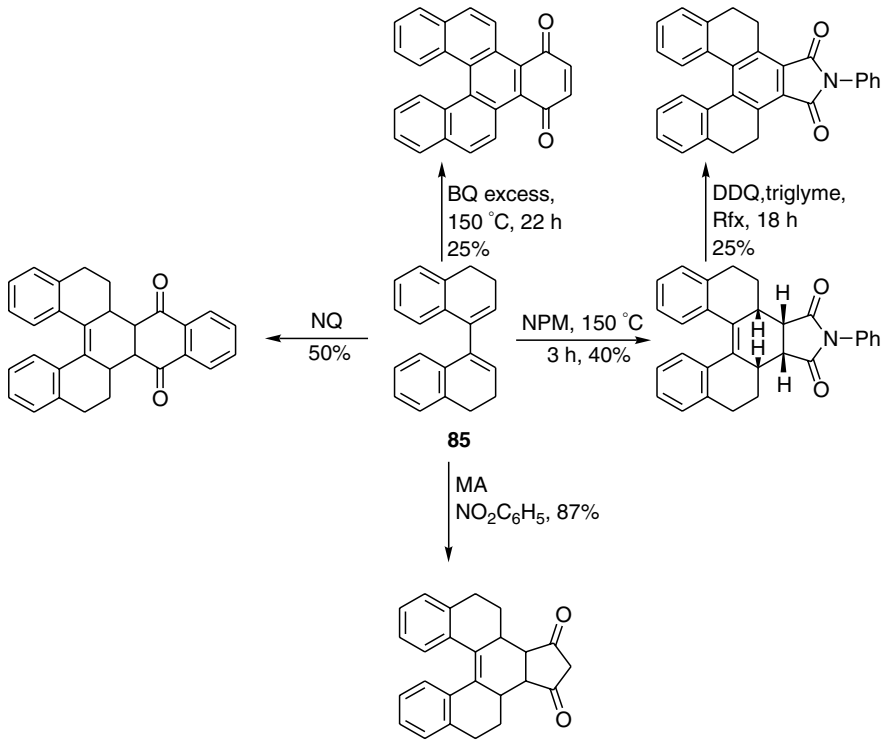
R_1	R_2	*exo/endo*
$PhSO_2$	Me	> 99:< 1
Me	Me	74:26
Me	Ph	> 99:< 1
Me		> 99:< 1

Scheme 2.37

DropBooks

2.2.6 Across-Ring Dienes

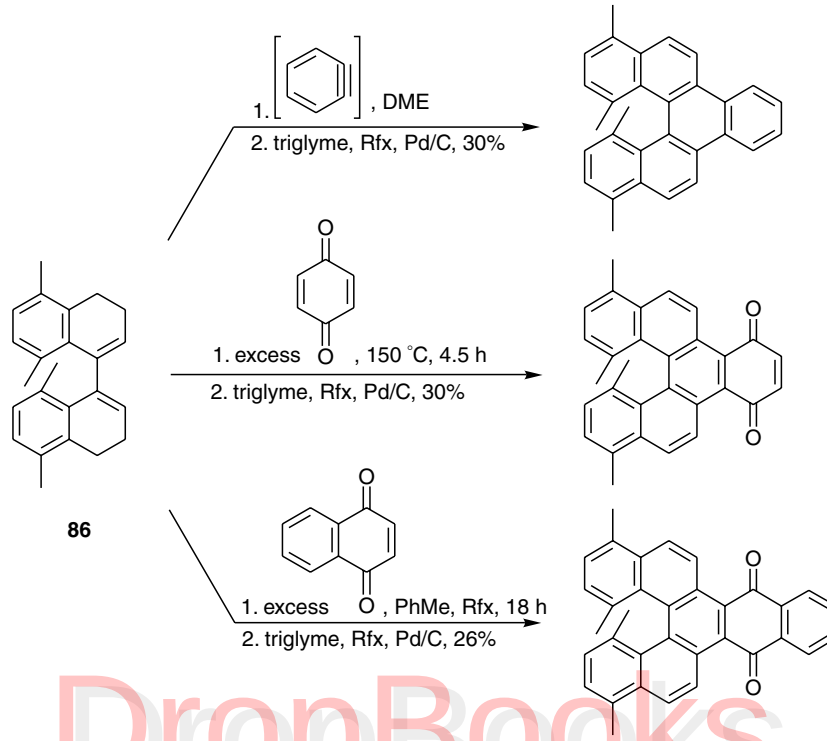
3,3′,4,4′-Tetrahydro-1,1′-binaphthalene (bisdialine) **(85)** is more reactive than the corresponding 1,1′-binaphthalene and has been used as a 4π component of cycloadditions to prepare very complex molecules. An improved method for preparing **85** was recently described [90]. The Diels–Alder reactions of **85** with a number of dienophiles were studied [90, 91] and are illustrated in Scheme 2.38.



BQ = 1,4-benzoquinone; NPM = N-phenylmaleimide; NQ = 1,4-naphthoquinone; MA = maleic anhydride

Scheme 2.38

Tetramethylbisdialine **86** has been used to synthesize substituted pentahelicenes characterized by a relatively high energy barrier to racemization due to the marked steric interactions between the methyl groups at the terminal aromatic rings [68b] (Scheme 2.39).



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Scheme 2.39

2.3 *HETERO*-DIELS–ALDER REACTIONS

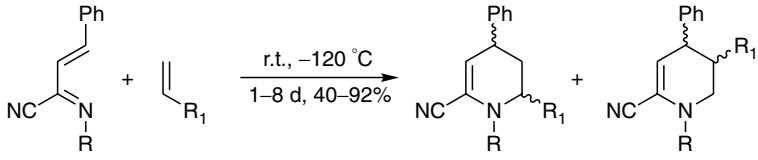
The *hetero*-Diels–Alder reaction permits heterocyclic-six- membered rings to be constructed by the interaction of heterodienes and/or heterodienophiles. Both the intermolecular and intramolecular versions of the *hetero*-Diels–Alder reaction are, therefore, very important methods for synthesizing heterocyclic compounds.

2.3.1 Heterodienes

Diels–Alder reactions of 1-azadienes are less thermodynamically favorable [92] than the all-carbon analogs because of the stronger carbon–nitrogen π-bond which is broken during the Diels–Alder reaction.

Reactivity of 1-azadienes **87** and the regioselectivity and stereoselectivity of the cycloadditions with dienophiles **88** are strongly dependent on the type of

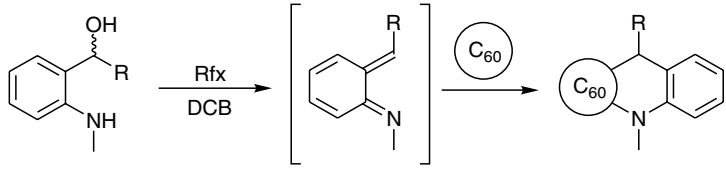
substituent at the nitrogen atom and on the nature of the dienophile. While azadiene **87a** was the most reactive, **87c** did not react and only the polymerization of the dienophile was observed [92] (Equation 2.24).



87 **88** (2.24)

a, R = CO_2Et R_1 = Ph, EtO, CO_2Me
b, R = Ph
c, R = OMe

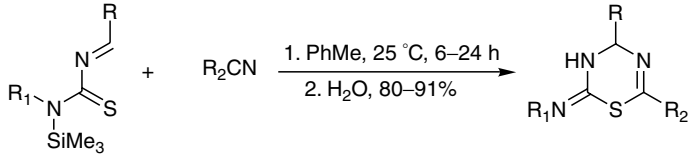
1-Azadienes **89**, generated *in situ* by thermolysis of the corresponding *o*-aminobenzylalcohols, have been used for the derivatization of [60]-fullerene through C–N bond formation leading to tetrahydropyrido [60]-fullerenes [93]. Theoretical calculations predicted these cycloadditions to be HOMO azadiene-controlled (Equation 2.25).



89 (2.25)

R = Ph, 2-Th, *p*-$MeOC_6H_4$

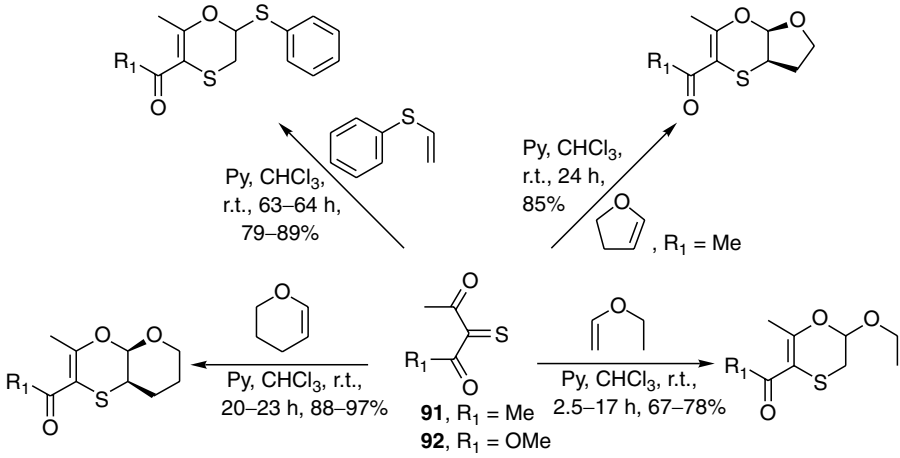
Thioazadienes **90**, formed *in situ* by the reaction of trimethylsilylimines and isothiocyanates, underwent cycloaddition reactions with nitriles bearing electron-withdrawing groups, to afford 1,3,5-thiadiazines [94] in excellent yield (Equation 2.26).



90 (2.26)

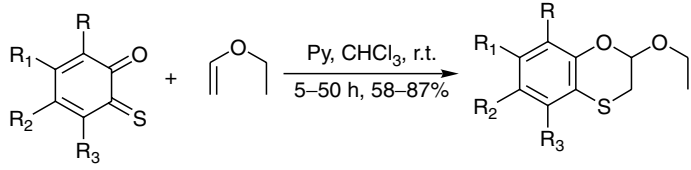
R = Ph, 2-Th; R_1 = Ph, *p*-ClC_6H_4; R_2 = Ts, CCl_3, CO_2Me

α, α′-Dioxothiones are another type of heterodienes that contain two heteroatoms. They are electron-poor dienes which are readily formed *in situ* and are then trapped by electron-rich alkenes. Cycloadditions of thiones **91** and **92** (Scheme 2.40) are regiospecific and chemospecific [95].



Scheme 2.40

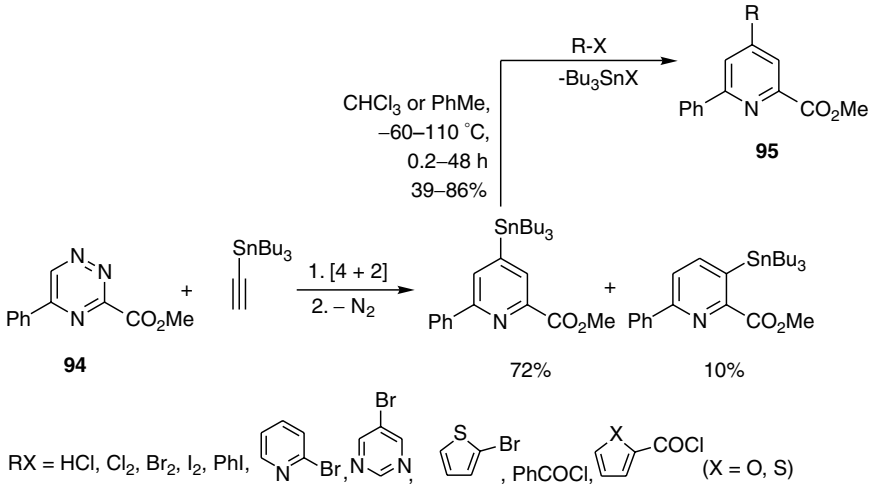
o-Thioquinones **93**, prepared simply from o-hydroxythiophthalimides, behave like α,α′-dioxothiones, affording a variety of complex heterocyclic compounds by inverse electron-demand Diels–Alder reaction [96] (Equation 2.27) with both vinyl ethers and electron-rich alkenes.



93 (2.27)

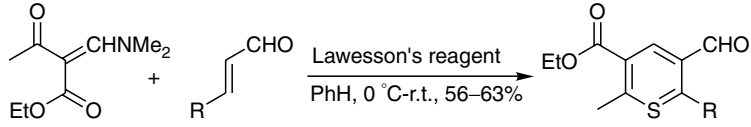
R = OH, OMe; R_1 = Me, OMe; R-R_1 = –(CH=CH)$_2$–; R_2-R_3 = (CH=CH)$_2$–;
R-R_1 and R_2-R_3 = –(CH=CH)$_2$–

Sauer and Heldmann [97] recently reported an interesting application of ethynyltributyltin as an electron-rich dienophile in an inverse electron-demand Diels–Alder reaction with the electron-deficient triazine derivative **94**. This method is interesting because the reaction is highly regioselective and the trialkylstannyl group is easily replaced by several groups under mild conditions, leading to substituted pyridines **95** (Scheme 2.41).



Scheme 2.41

The combination of thionation by Lawesson's reagent [98] of oxoenaminoketones **96** with normal electron-demand Diels–Alder reaction of conjugated aldehydes allows a variety of thiopyrans **97** to be synthesized by a regioselective and chemoselective one-pot methodology [99] (Equation 2.28). Thionation occurred at the more electrophilic ketonic carbonyl group.



(2.28)

The thionation–cycloaddition sequence is accompanied by the elimination of dimethylamine from the cycloadduct to afford thiopyrans. Similarly, when the thionation–cycloaddition methodology was applied to enaminoketones **98** and **99**, obtained from thiochromanones, tricyclic compounds **100** and **101** were obtained (Figure 2.12).

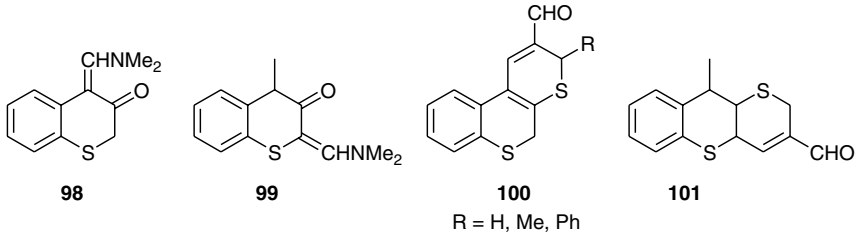
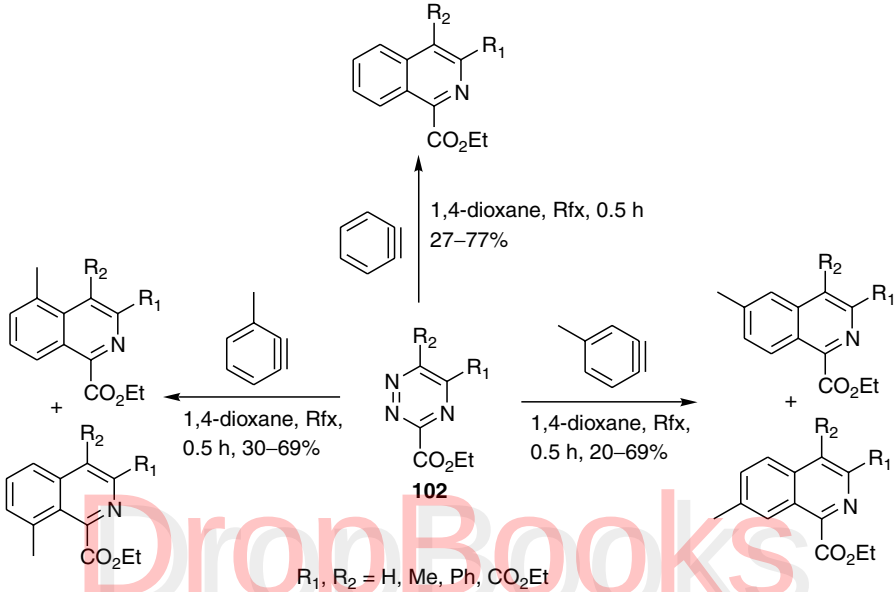


Figure 2.12

A Diels–Alder reaction of arynes with 1,2,4-triazines **102** allows the preparation of isoquinolines substituted with electron-withdrawing groups in the nitrogen-containing ring. The isoquinoline-1-carboxylic esters bearing additional substituents are of particular interest because they are not readily available by the usual routes [100,101] (Scheme 2.42).



Scheme 2.42

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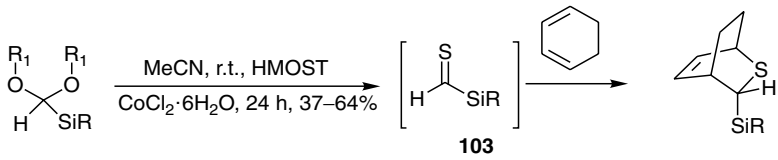
2.3.2 Heterodienophiles

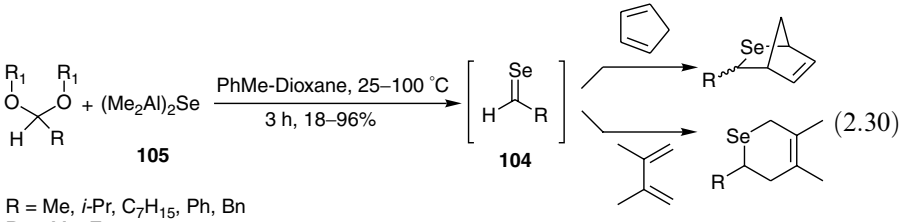
Silylthioaldehydes **103**, reactive dienophiles formed *in situ* from acetals according to a general method, are directly trapped with dienes to afford sulfur-containing heterocyclic compounds in good yield (Equation 2.29). Silylthioaldehydes are quite reactive in comparison with the aliphatic ones [102] which are rather inert in the cycloaddition reactions.



(2.29)

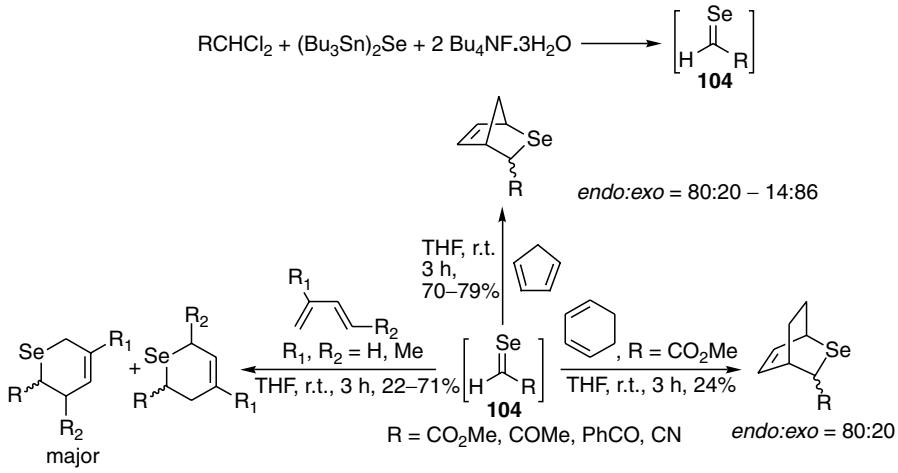
R = Me_3, Et_3, *t*-$BuMe_2$, $PhMe_2$, Ph_2Me
R_1 = Me,
R_1-R_1 = $-(CH_2)_3-$

Selenoaldehydes **104**, like thioaldehydes, have also been generated *in situ* from acetals and then directly trapped with dienes, thus offering a useful one-pot procedure for preparing cyclic seleno-compounds [103,104]. The construction of a carbon–selenium double bond was achieved by reacting acetal derivatives with dimethylaluminum selenide (Equation 2.30). Cycloadditions of seleno aldehydes occur even at 0 °C. In these reactions, however, the carbon–selenium bond formed by the nucleophilic attack of the electronegative selenium atom in **105** to the aluminum-coordinated acetal carbon, may require a high reaction temperature [103]. The cycloaddition with cyclopentadiene preferentially gave the kinetically favorable *endo* isomer.



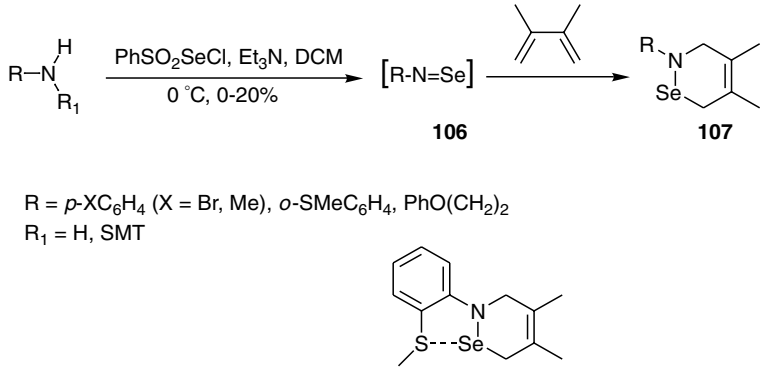
(2.30)

Selenoaldehydes have also been obtained by reacting chlorocarbonyl compounds with selenide ions generated by a fluorodestannylation technique using $(Bu_3Sn)_2Se$ and $Bu_4NF{\cdot}3H_2O$ [105]. Selenoaldehydes **104** bearing an electron-withdrawing group such as CO_2Me, COMe, COPh or CN were efficiently prepared and trapped by dienes, whereas when R was Ph or MeO groups, selenoaldehydes were not generated (Scheme 2.43).



Scheme 2.43

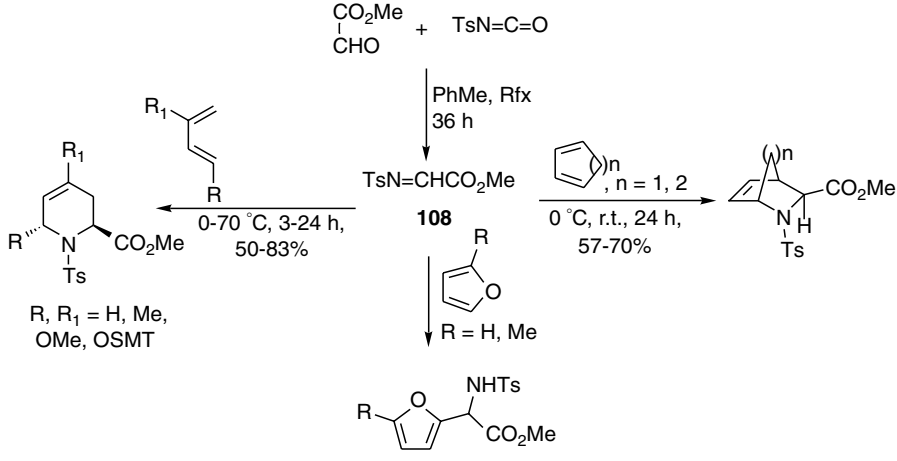
A carbon–selenium bond can also be formed [106] by Diels–Alder reaction of the transient selenonitroso species **106** generated by phenylsulfinylselenylchloride reacting with amines or trimethylsilylated amines. Selenonitroso compounds **106** were trapped with 2,3-dimethylbutadiene to afford 1,2-selenazine derivatives **107** (Scheme 2.44) in low yield. 1,2- Selenazines are interesting compounds which are quite unstable (2–3 h), except for the one having an



Scheme 2.44

ortho-thiophenyl-substituent which presumably increases the stability (3 days) by virtue of a nonbonded five-membered ring S···Se interaction [107].

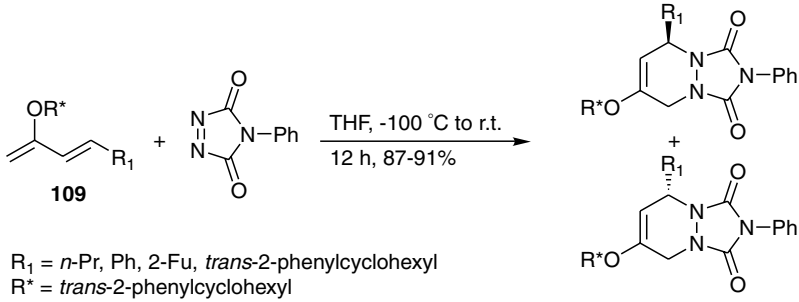
Diels–Alder reaction of tosylimine **108** obtained by thermal [2+2] cycloaddition of *p*-toluensulphonylisocyanate and methylglioxylate [108] provides a method for synthesizing nitrogen-containing heterocycles. The tosylimine was not isolated but was used directly *in situ* in several cycloaddition reactions (Scheme 2.45) which were completely regioselective [109]. In the case



Scheme 2.45

of furan and 2-methyl furan, only electrophilic aromatic substitution at the α-position was observed.

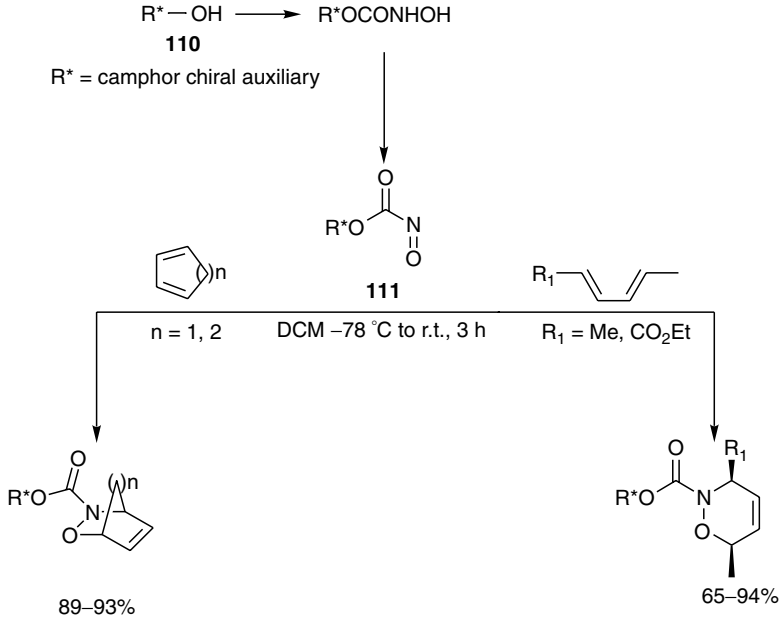
The cycloaddition of chiral, racemic and non-racemic alkoxybutadienes **109** with phenyltriazolinedione led to aza compounds [110] in high yield, with good facial selectivity (diastereomeric excess: 87–92 %) (Equation 2.31). The cycloadditions of the same dienes with N-phenylmaleimide require Lewis acid catalysis.



(2.31)

R_1 = *n*-Pr, Ph, 2-Fu, *trans*-2-phenylcyclohexyl
R* = *trans*-2-phenylcyclohexyl

Chiral heterocyclic compounds containing vicinal oxygen and nitrogen atoms were achieved by an asymmetric Diels–Alder reaction [111] of chiral acylnitroso dienophiles **111**. The latter were prepared *in situ* from alcohols **110**, both antipodes of which are available from camphor, and trapped with dienes (Scheme 2.46). Both the yield (65–94 %) and diastereoisomeric excess (91–96 %) were high.



Scheme 2.46

2.4 INTRAMOLECULAR DIELS–ALDER REACTION

A Diels–Alder reaction can also take place intramolecularly when a molecule incorporates both the diene and dienophile moieties which are connected by a chain. Nowadays the intramolecular Diels–Alder reaction is a valuable tool in organic synthesis because it allows two rings, of which only one is formed by the [4+2] cycloaddition, and up to four new chiral centers to be formed in one step [112]. Both carbocyclic and heterocyclic rings may be generated depending on the nature of the interacting moieties; the size of the second ring depends on chain broadening.

Wulff and Powers [113] developed a methodology for preparing bicyclic esters by intramolecular cycloaddition reactions of (E,E) and (Z,E)-deca-2,7,9-trienyl (**112a** and **113a**) and undeca-2,9,11-trienyl (**112b** and **113b**) pentacarbonyltungsten and tetracarbonyltriphenylphosphinetungsten carbene complexes as ester synthons. Some of the results are summarized in Schemes 2.47 and 2.48. The reactions of (E,E)- compounds are highly *endo*-diastereoselective and the observed diastereoselectivity was far superior to that afforded by thermal cycloadditions of the corresponding organic esters. Facile oxidation of the resulting complexes using cerium(IV) occurred with the retention of the stereochemistry to afford the corresponding esters.

Feringa-butenolide **114,** in the presence of Dess–Martin periodinane reagent and 2,6-lutidine, gave the bis-ketone **115** which underwent intramolecular cycloaddition to afford *endo*-selectively the desired decalin-based lactone **116** (Equation 2.32) [114]. Double activation of butenolidic double bond strongly increases the reactivity of dienophile **115**.

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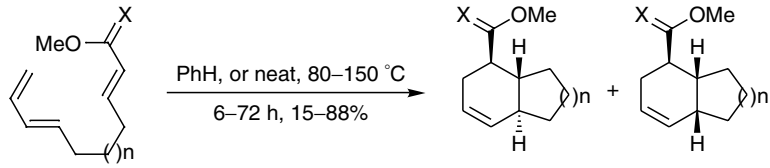
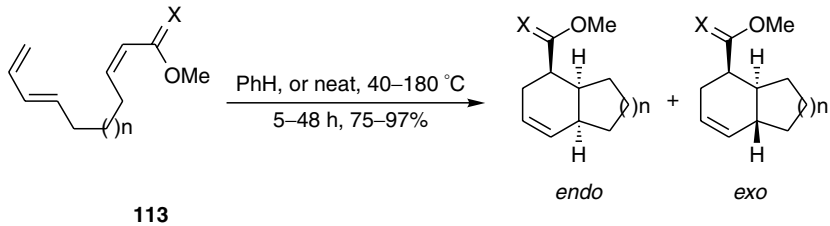


112
a, n = 1; **b**, n = 2

X	**112**	*endo:exo*
$W(CO)_5$	**a**	98:2
	b	93:7
O	**a**	60:40
	b	51:49
$W(CO)_4PPh$	**a**	94:6
	b	88:12

Scheme 2.47



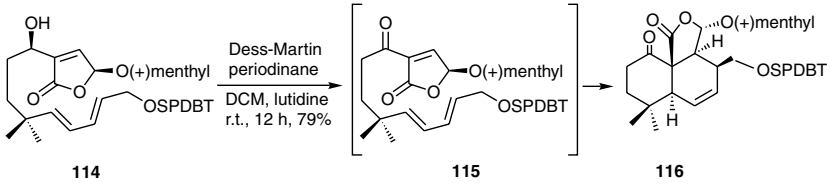
113

a, n = 1; **b**, n = 2

X	**113**	*endo:exo*
$W(CO)_5$	**a**	45:55
	b	78:22
O	**a**	35:65
	b	49:51

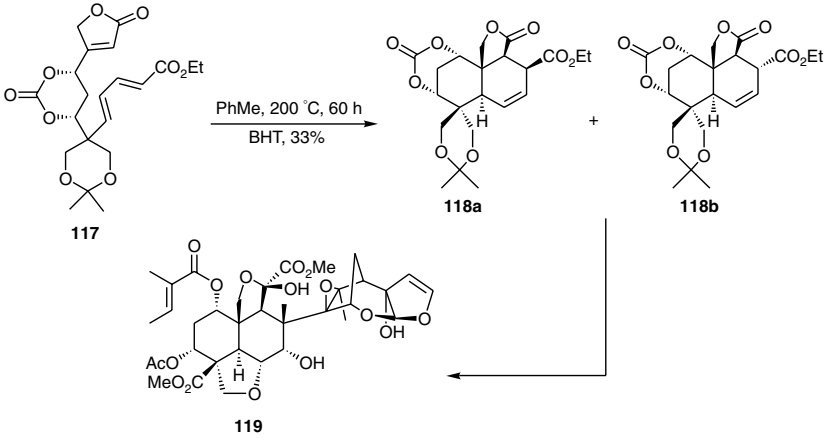
Scheme 2.48

An intramolecular cycloaddition reaction of **117** is the crucial step in the synthesis of the highly functionalized decalin [115] moiety of azadirachtin **119**.

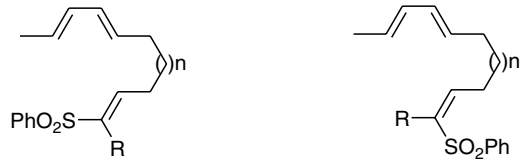


114 **115** **116** (2.32)

Cycloaddition occurred by heating compound **117** at 200 °C in a sealed tube. This led to products **118,** both of which may be versatile intermediates for the total synthesis of **119** (Equation 2.33).



117 **118a** **118b** **119** (2.33)

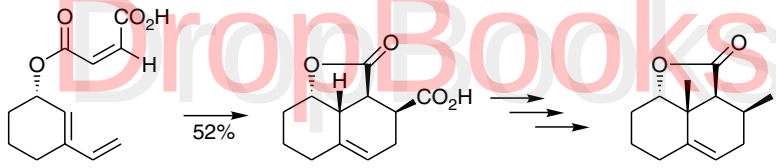


120a **120b**

Figure 2.13

The extensive study of Craig and coworkers [116] on the intramolecular Diels–Alder reactions of E- and Z-sulphonyl-substituted deca-, undeca- and dodecatrienes **120** (Figure 2.13) has opened a short route to *trans*- and *cis*-bridgehead hydrindanes and decalines and has given new insights into the role of dienophile substitution and geometry in determining the stereochemical outcome of these intramolecular cycloadditions.

Decalin unit **121**, an intermediate in the total synthesis of compactin, has been prepared by intramolecular cycloaddition reaction [117] of trienone-carboxylic acid **122** carried out under either thermal conditions or microwave irradiation. The desired *exo*-adduct **123** was the major stereoisomer (Equation 2.34). Similar results were observed in the cycloadditions of the corresponding esters.



122 **123** **121** (2.34)

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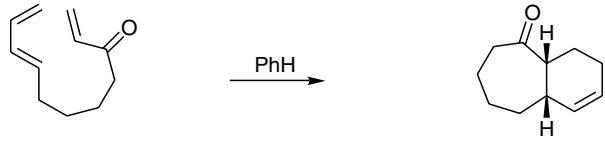
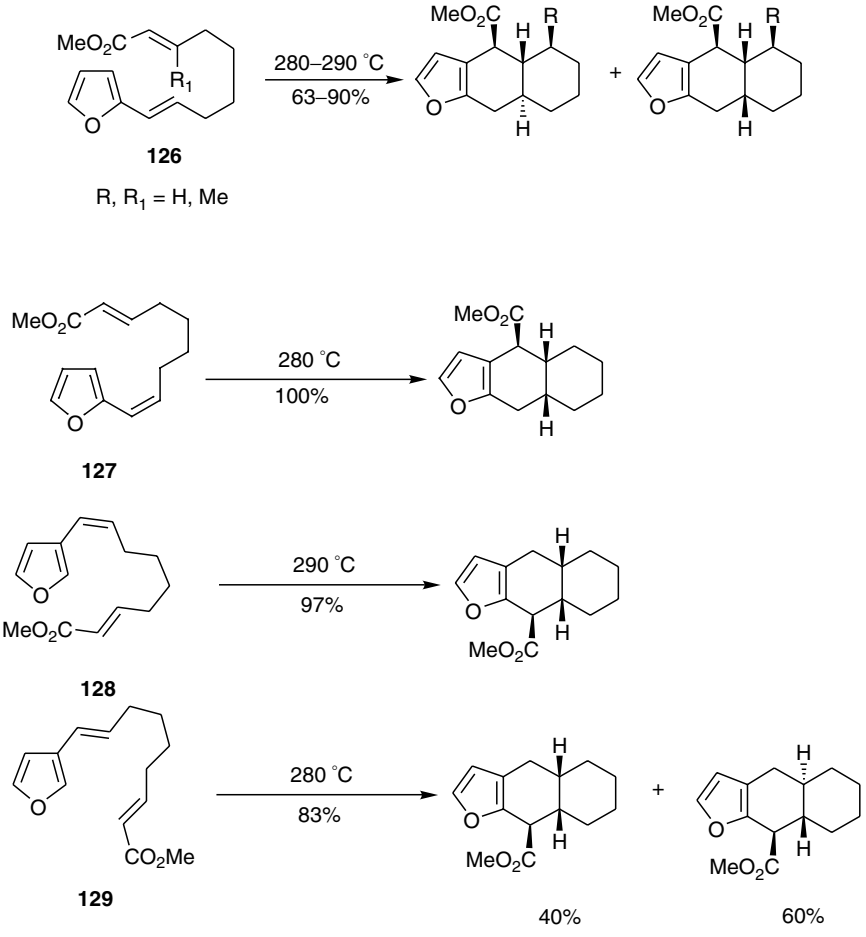
Trienone **124** underwent intramolecular cycloaddition affording hydrobenzosuberone **125**. Thermal reaction was poorly diastereoselective (62:38 *cis*:*trans* stereoisomers). When the cycloaddition was carried out in the presence of $LiBF_4$, trienone **124** was converted into *cis*-adduct **125** quantitatively and stereoselectively [118] (Equation 2.35).



124 **125** (2.35)

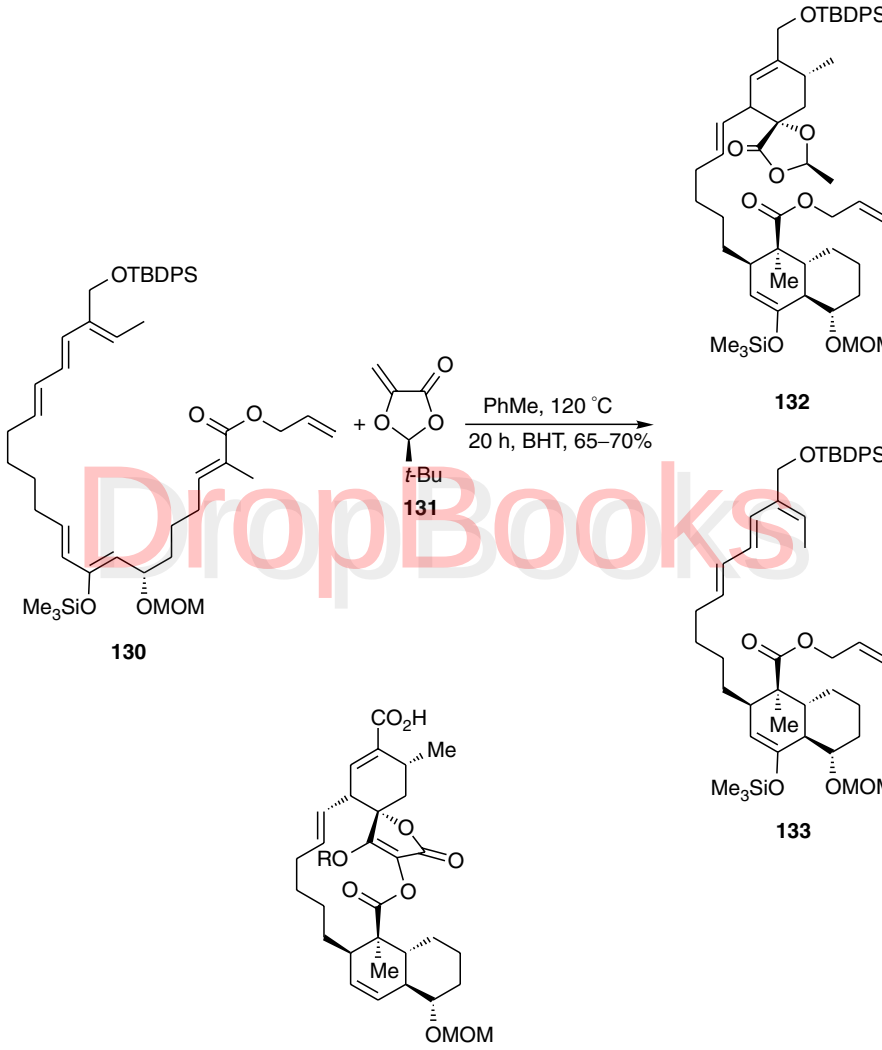
Cat.	*T* (°C)	*t* (h)	Yield (%)	*cis/trans*
-	155	5	90	62:38
$LiBF_4$	25	72	100	100:0

Furanodecalins can be readily obtained by intramolecular cycloadditions of 2-furylnonadienoates **126, 127**, and 3-furylnonadienoates **128, 129**. These vinylfurans reacted intramolecularly and selectively across the diene unit which includes the vinylsubstituents. Thermolysis [119] of (E,E) and (Z,E) 2-furylesters **126** and **127** gave a mixture of *cis*- and *trans*-bridgehead furanodecalins with a slight preference for the *trans*-isomers, and *cis*-furanodecalin alone, respectively (Scheme 2.49). As expected the stereochemistry of the dienoates **126** and **127** controlled the stereochemistry of the ring junction. Thermolysis of (Z,E)-3-furyl **128** and (E,E)-3-furyl **129** dienoates afforded *cis*-furanodecalins with a different regiochemistry of the ester functionality. The *cis*-furanodecalin ring system is characteristic of naturally occurring sesquiterpenes [120].



Scheme 2.49

(−)-Chlorothricolide, the aglycon of the chlorothricin antibiotic, is a complex molecule containing an octahydronaphthalene unit. Roush and Sciotti [121] recently reported the total enantioselective synthesis of chlorothricolide. The multiple Diels–Alder reaction between poliene **130** and chiral dienophile (R)-**131** was the key step in the synthetic process (Scheme 2.50). The interaction



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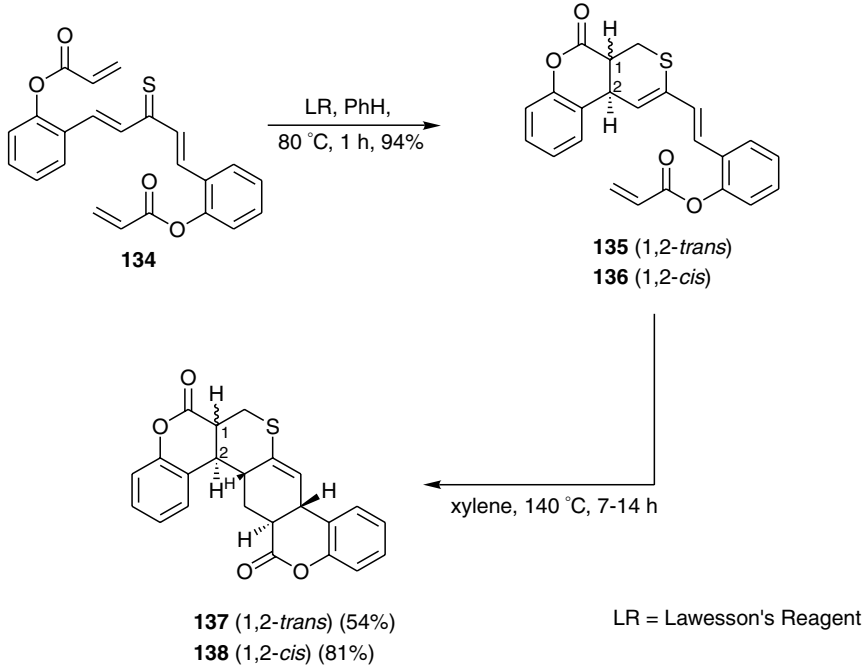
Scheme 2.50

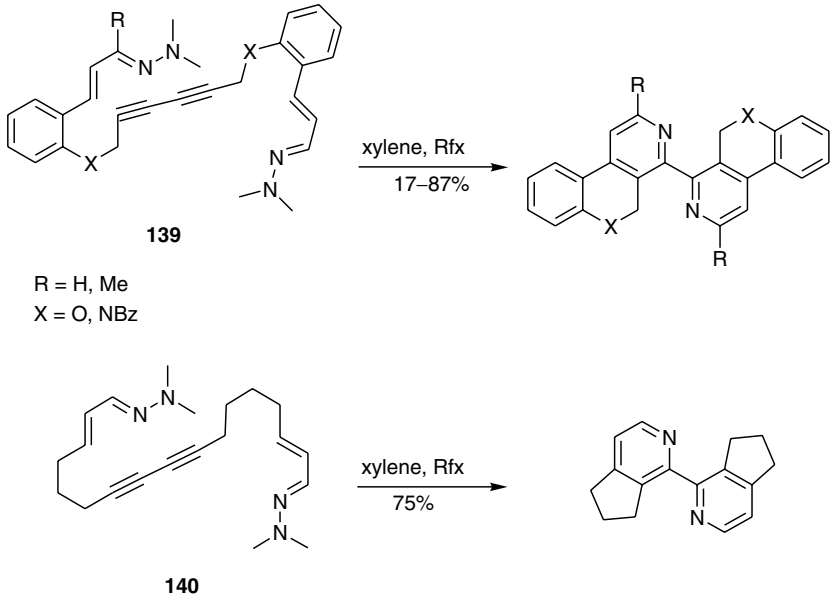
between **130** and **131** gave two main products, the desired **132** and **133**; the latter was recycled further to give **132**.

A sequence of two thermal intramolecular cycloadditions has been used to develop a short synthetic approach to tetrahydrothiopyrans [122]. The multiple process includes an intra-*hetero*- and an intramolecular-carbon Diels–Alder reaction. An intramolecular *hetero*-Diels–Alder reaction of divinylthioketone **134** afforded a 9:1 mixture of cycloadducts **135** and **136** which then underwent a second intramolecular cycloaddition which *syn*(to H-2)-*exo*-diastereoselectively led to hexacyclic tetrahydrothiopyrans **137** and **138**, respectively (Scheme 2.51).



Scheme 2.51

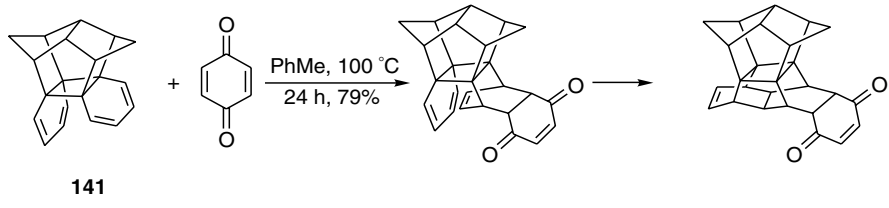
Double intramolecular *hetero*-Diels–Alder reaction of 1,3-diynil-bis-α,β-unsaturated hydrazones **139** and **140** is a good example of a thermal multiple Diels–Alder reaction and is a particularly attractive route to annelated pyridines [123]. The initial cycloadduct readily aromatizes by the loss of dimethylamine (Scheme 2.52) under thermal reaction conditions.



Scheme 2.52

There is another type of multiple thermal Diels–Alder reaction in which the initial monoadduct is involved, either directly or after one transformation, in a second cycloaddition that affords the final polycyclic compounds. These methodologies have been used especially in the synthesis of polycyclic cage compounds. Paquette was the first to report the conversion of 9,10-dihydrofulvalene into polyfused cyclopentanoid systems [124].

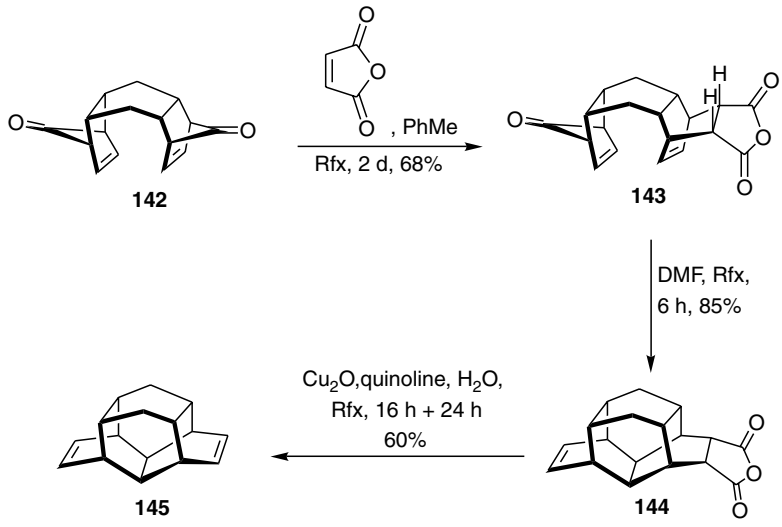
Tetraene **141** has been converted into various complex polycondensed adducts by reacting with a variety of dienophiles such as maleic anhydride, N-phenylmaleimide, N-phenyltriazolinedione, *p*-benzoquinone and tetracyanoethylene carried out under thermal conditions. All cycloadditions occurred facial-diastereoselectively from an outside attack and provided monocycloadducts which had an exceptionally close relationship between diene and dienophile and then underwent intramolecular cycloaddition [125]. The reaction between **141** and *p*-benzoquinone is illustrated in Scheme 2.53.



141

Scheme 2.53

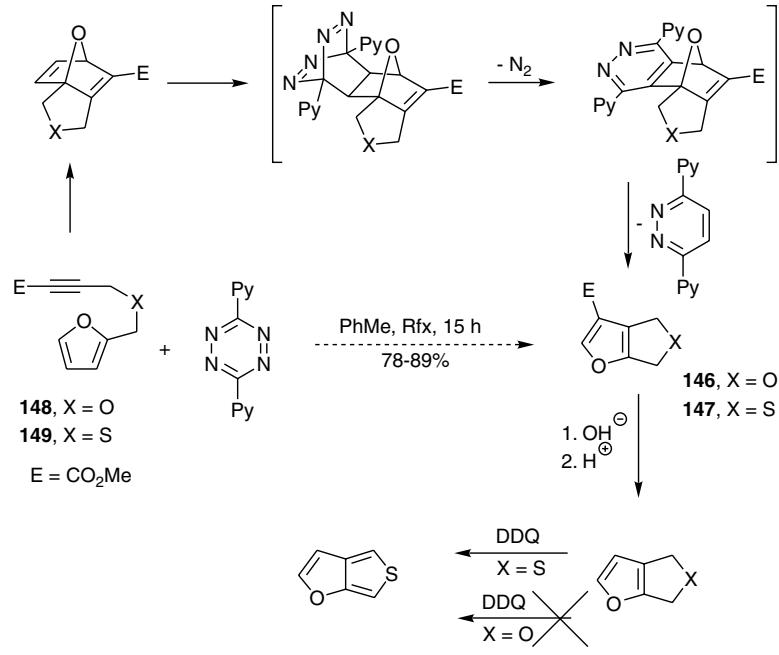
The synthesis of polycyclic diene **145** is another good example of this methodology [126]. Structurally, polycyclic cage compound **145** embeds the carbon skeleton of secohexaprismane [127] and iceane [128] and may serve as a synthetic precursor of these two-ring systems (Scheme 2.54). Treating the known bis-dienone **142** with maleic anhydride in toluene at reflux temperature leads to cycloadduct **143** as a result of thermal decarbonylation followed by cycloaddition with the diene generated *in situ*. Decarbonylation of **143,** followed by a second intramolecular Diels–Alder reaction, furnished caged hexacyclic ene anhydride **144** which was then converted into compound **145** by treating it with Cu_2O in hot quinoline in the presence of 2,2′-bipyridine and a small amount of water.



Scheme 2.54

A complex sequence of pericyclic reactions, intramolecular and intermolecular cycloadditions and cycloreversions, was studied in an attempt to readily achieve bicyclic five-membered heterocycles, the methyl 4,6-dihydrothieno- and methyl-4,6-dihydrofuro[3,4-b]-furan-3-carboxylates **146** and **147**. The results give further evidence of the potential of intramolecular Diels–Alder based multiple processes [129]. 2-Substituted furans and thiophenes **148** and **149**, heated in the presence of 3,6-di(pyridin-2′-yl)-*s*-tetrazine, underwent intramolecular and intermolecular cycloadditions. The cycloadducts underwent double cycloreversion reactions with the loss of a nitrogen and dipyridyldiazine as illustrated in Scheme 2.55. The electron-deficient dipyridyltetrazine reacts with the isolated, electron-rich olefinic bond rather than with the bond conjugated with the methylcarboxylate.

In addition to the multiple processes involving two Diels–Alder reactions in *intra–intra, inter–intra* or *inter–inter* molecular sequences, other processes have



Scheme 2.55

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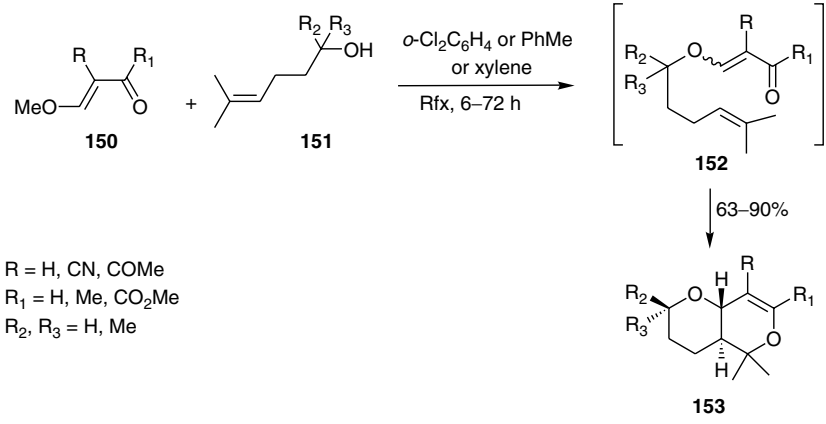
been developed, including one Diels–Alder reaction in sequence with another reaction. This thus increases the synthetic potential of the thermal intramolecular Diels–Alder methodology. A significant example is the recently described procedure for synthesizing bicyclic heterocycles which is based [130–132] on the transetherification-intramolecular *hetero*-Diels–Alder reaction. It is a one-pot procedure (Scheme 2.56) in which activated α, β-unsaturated carbonyl

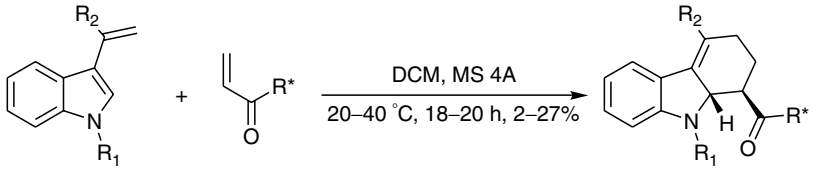


Scheme 2.56

compounds **150** interact with δ,ε-unsaturated alcohols **151** under thermal conditions giving the intermediate **152** which affords stereoselectively hydropyranopyran derivatives **153** in good yields.

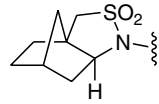
2.5 OUTLINED DIELS–ALDER REACTIONS

First asymmetric Diels–Alder reactions in the vinylhetarene series: cycloaddition with vinylindoles to enantiomerically pure carbazole derivatives [133]

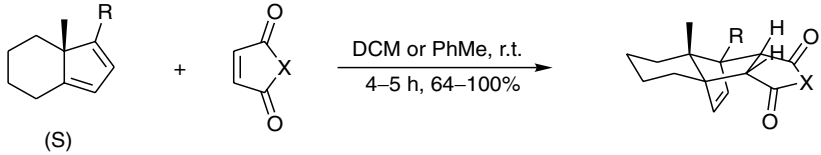


R_1 = $PhSO_2$, Me; R_2 = Ph, Me

6 dienes: 3-vinylindoles and 2-vinylindoles

R* = 

Face-selective and *endo*-selective cycloaddition with enantiomerically pure cyclopentadienes [134]

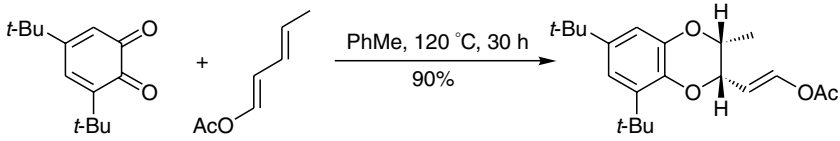


(S)

(both enantiomers R and S)

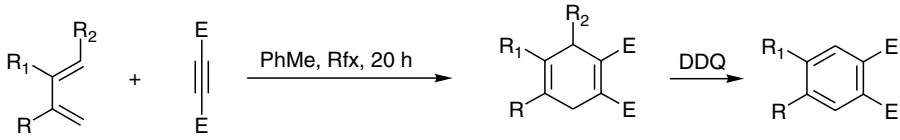
X = O, NH; R = Ph, *p*-$MeOC_6H_4$, *o*-$MeOC_6H_4$, 2,4-$(MeO)_2C_6H_3$, 2-Naphthyl

Hetero-Diels–Alder reactions of 3,5-di-*tert*-butyl-*o*-benzoquinone with acyclic dienes: novel synthesis of 1,4-benzodioxanes [135]



4 dienes

Synthesis of functionalized aryloxy 1,3-butadienes and their transformation to dienyl ethers via Diels–Alder cycloaddition reactions [136]

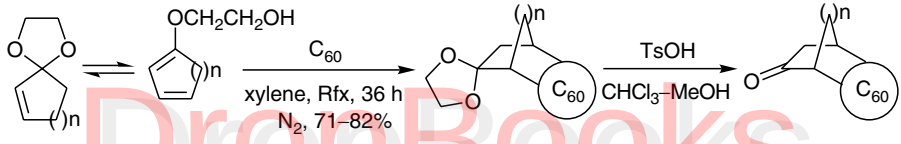


R = Me, OMe, OTMS; R_1 = OPh, *p*-MeC_6H_4;
R_2 = SBu, OSMT E = CO_2Me

overall yield: 40-92%

5 dienes, 3 acetylenic dienophiles

Highly thermally stable Diels–Alder adducts of [60]-fullerene with 2-cycloalkenones and their acetals [137]



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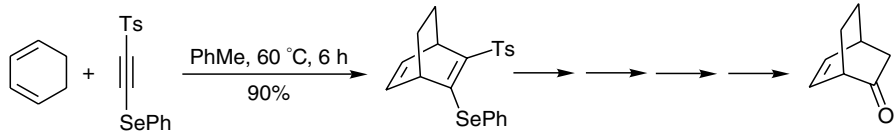
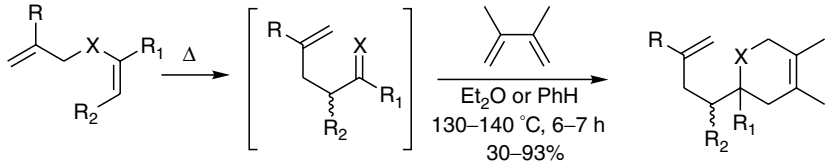
Diels–Alder reactions of 1-(phenylseleno)-2-(*p*-toluensulphonyl)ethyne: a novel dienophile and ketene equivalent [138]



7 acyclic and cyclic dienes

Generation of a selenoaldehyde, a selenoketone, and telluroaldehydes by [3,3] sigmatropic rearrangement of allyl alkenyl selenides and tellurides [139]



R = H, Me; R_1 = H, Ph; R_2 = Ph, CO_2Me, 4-$CF_3C_6H_4$; X = Se, Te

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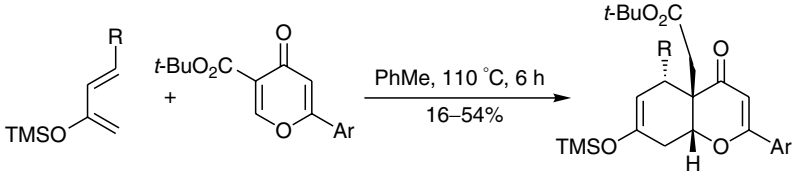
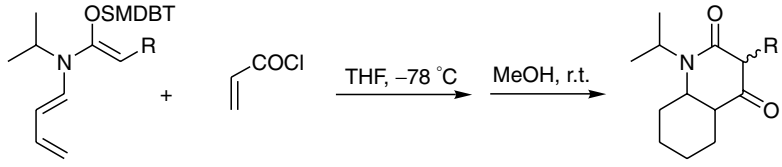
An efficient synthesis of reduced flavones via Diels–Alder addition to 4H-pyran-4-ones [140]



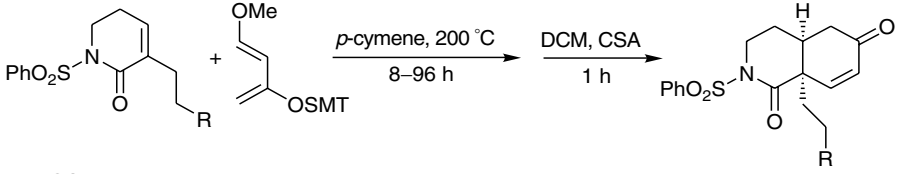
R = H, OMe; Ar = Ph, *p*-$MeOC_6H_4$

Preparation of N-alkylketene-N-butadienyl-N,O-silyl acetals [141]



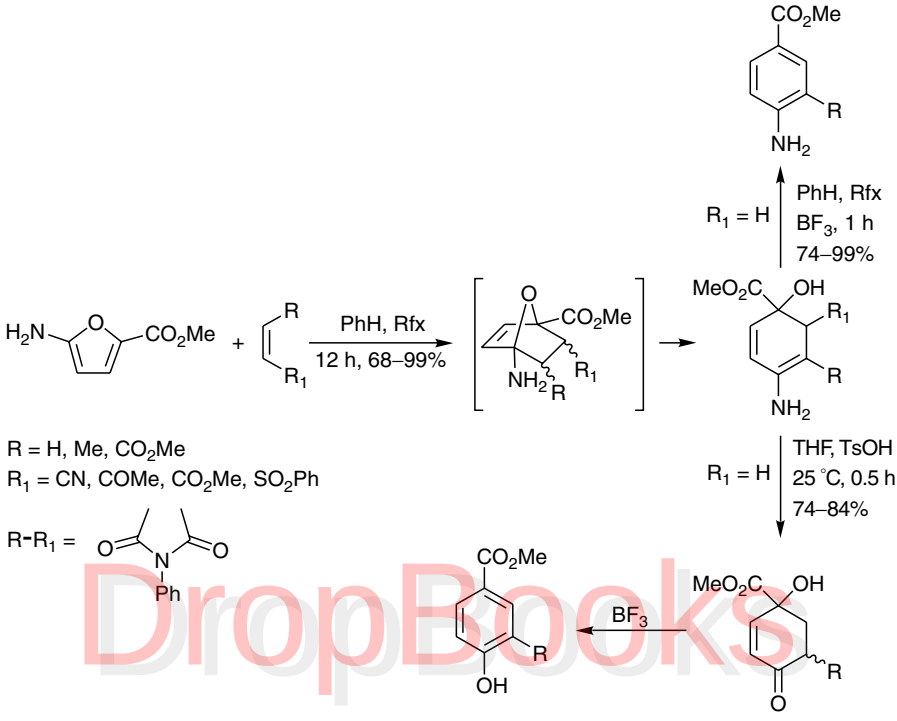
R = Me, Ph, *p*-$MeOC_6H_4$

Diels–Alder reaction of the dihydropyridinones V: approach to the Ircinal B core [142]



R = CO_2Me, $(CH_2)_3$-CN

Synthesis of polysubstituted anilines using the Diels–Alder reaction of methyl-5-aminofuroate [143]



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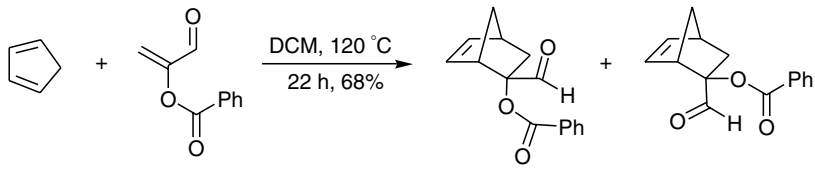
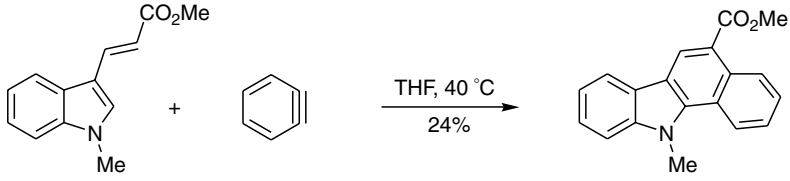
Preparation and Diels–Alder cycloaddition of 2-acyloxyacroleins. Facile synthesis of functionalized taxol A-ring synthons [144]

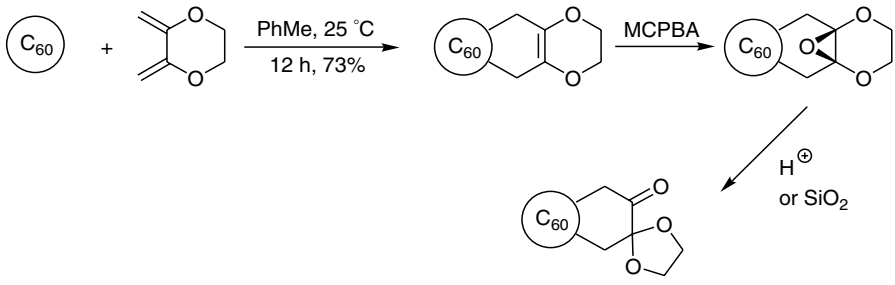


New Diels–Alder reactions of 3-vinylindoles with an aryne: selective access to functionalized [a]anellated carbazoles [145]

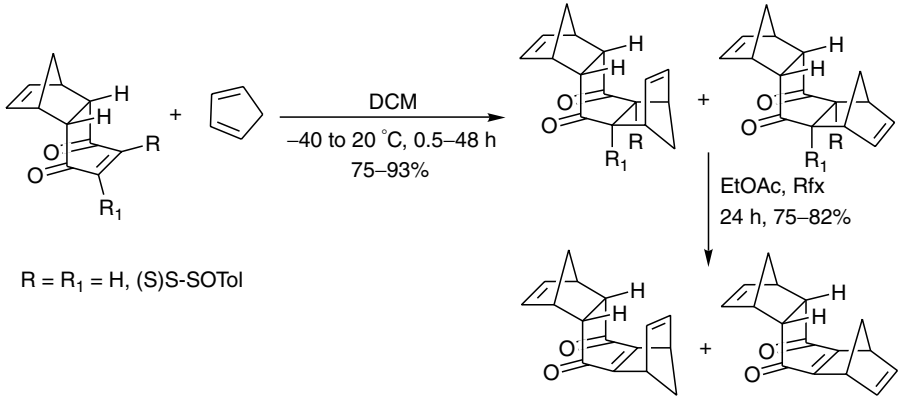


4 vinylindoles; 2 arynes

Exohedral functionalization of [60]-fullerene by $[4+2]$ cycloadditions. Diels–Alder reactions of [60]-fullerene with electron-rich 2,3-dioxysubstituted-1,3-butadienes [146]

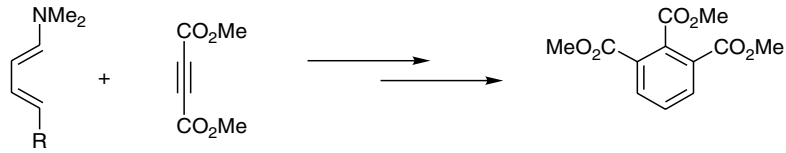


Studies of diastereoselectivity in Diels–Alder reactions of (S)S-4*a*,5,8,8*a*-tetrahydro-5,8-methane-2-(*p*-tolysulfinyl)-1,4-naphthoquinones with cyclopentadiene [147]



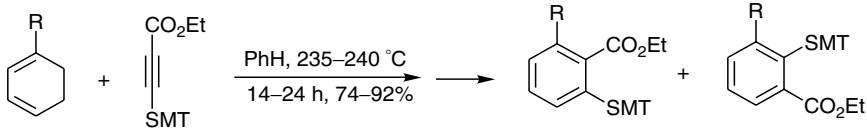
R = R_1 = H, (S)S-SOTol

Aminodienylesters. I: the cycloaddition reactions of *tert*-aminodienylester with α,β-unsaturated carbonyl compounds, styrenes and quinones [148]



R = CO_2Me, CN 16 dienophiles xylene, r.t. or Rfx, 0.5–28 h, 10–95%

Diels–Alder reactions of 1,3-cyclohexadienes and 3-(trimethylsilyl)propynoates. A new synthesis of *ortho*-(trimethylsilyl)benzoate esters [149]



R = H, OMe

First stereoselective [4 + 2] cycloaddition reactions of 3-cyanochromone derivatives with electron-rich dienes: an approach to the ABC tricyclic frame of arysugacin [150]

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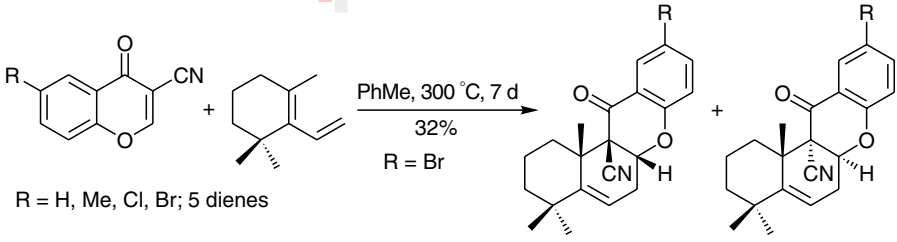
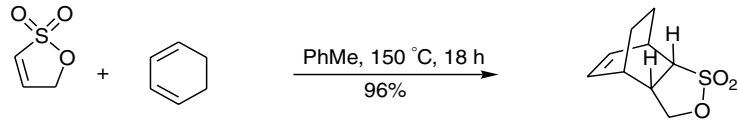


R = H, Me, Cl, Br; 5 dienes

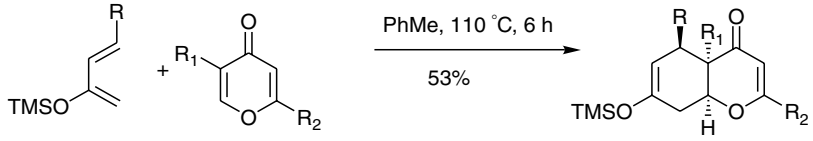
86 14

Synthesis and Diels–Alder reactions of α,β-unsaturated γ-sultone [151]



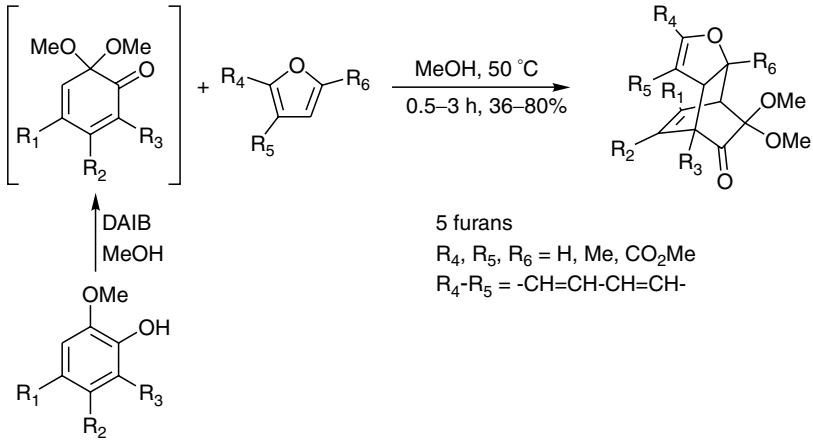
7 dienes

Synthesis and reactions of reduced flavones [152]



R = H, OMe; R_1 = CO_2Bn, CO_2t-Bu; R_2 = Ph, p-$MeOC_6H_4$

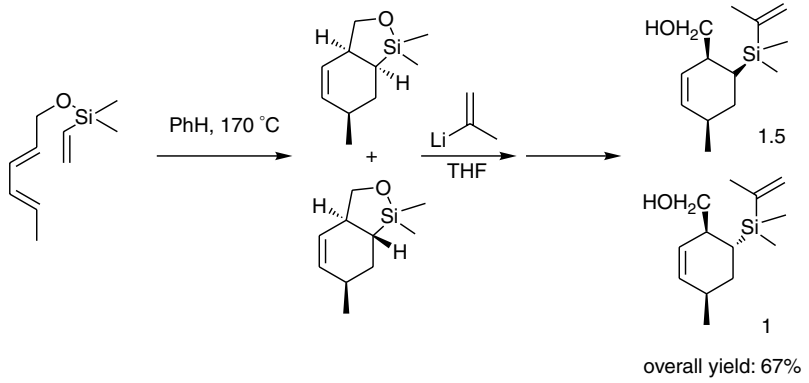
Furans act as dienophiles in facile Diels–Alder reactions with masked *o*-benzoquinones [153]



5 furans
R_4, R_5, R_6 = H, Me, CO_2Me
R_4-R_5 = -CH=CH-CH=CH-

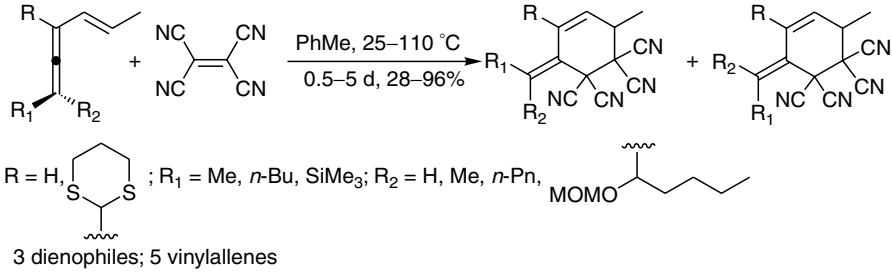
R_1 = H, CO_2Me, COMe; R_2 = H, CO_2Me; R_3 = H, OMe

Oxasilacyclopentanes as intermediates for silicon tethered ene cyclizations [154]



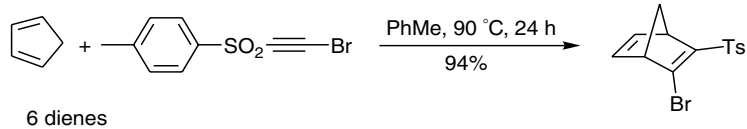
overall yield: 67%

Stereoselective construction of tetrasubstituted exocyclic alkenes from the [4 + 2] cycloaddition of vinylallenes [155]



3 dienophiles; 5 vinylallenes

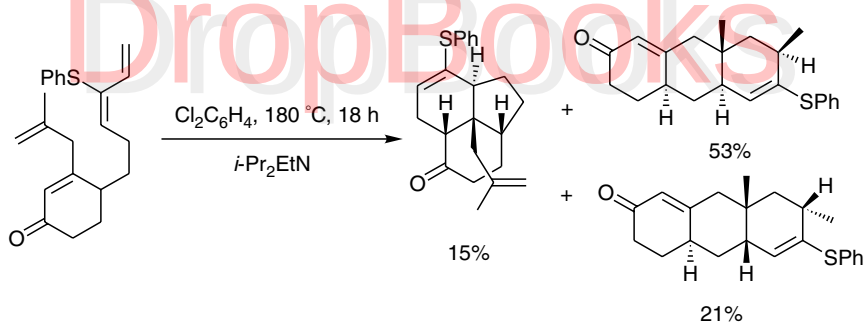
2-Bromoethylvinylarylsulfones as versatile dienophiles: a formal synthesis of epibatidine [156]



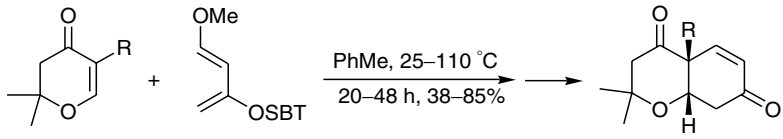
6 dienes

Anomalous products from the thermal Diels–Alder reaction of a (E)-2-thiophenylbutadiene tethered to 3-methallylcyclohexenone [157]

DropBooks

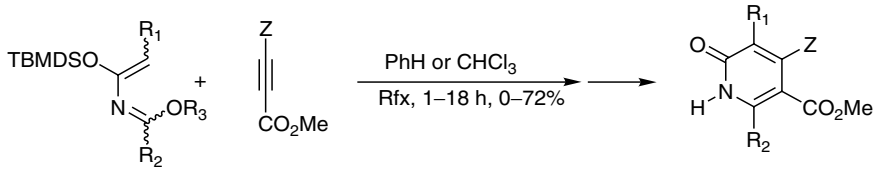


Dihydropyrones as dienophiles in the Diels–Alder reaction: application to the synthesis of 1-oxadecalones [158]



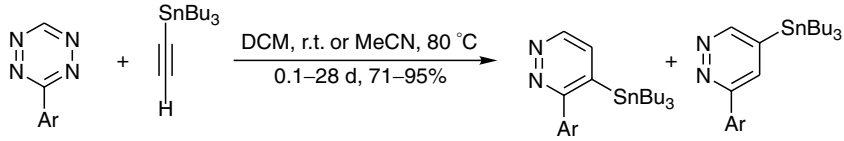
R = CN, COMe, CO_2Et, SO_2Ph
6 dienes

A highly efficient multicomponent synthesis of pyridones and pyrimidones by a $[2 + 2 + 2]$ strategy [159]



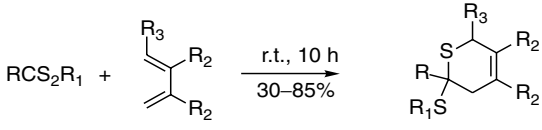
R_1 = H, Me, Bu, Ph, F, Cl; R_2 = H, Me;
R_3 = TBDMS, *i*-Pr, Et; Z = H, Me, CO_2Me
9 dienes, 8 dienophiles

Synthesis of 3,5-disubstituted pyridazines by regioselective $[4 + 2]$ cycloadditions with ethynyltributyltin and subsequent replacement of the organotin substituent [160]



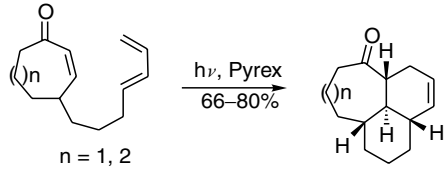
18 aryl-1,2,4,5-tetrazines

Synthesis of alkyl perfluoroalkanedithiocarboxylates and some aspects of their reactivity in cycloaddition reactions [161]



R = CF_3, C_3F_7; R_1 = Et, Bn
2 dienes: R_3 = H, R_2 = Me; R_2 = H, R_3 = OSMT

The intramolecular Diels–Alder reactions of photochemically generated *trans*-cycloalkenones [162]



n = 1, 2

6 substrates

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3 Lewis-Acid-Catalyzed Diels–Alder Reaction

3.1 INTRODUCTION

The terms acid and base have been defined in different ways depending on the particular way of looking at the properties of acidity and basicity [1]. Arrhenius first defined acids as compounds which ionize in aqueous solution to produce hydrogen ions, and bases as compounds which ionize to produce hydroxide ions. According to the Lowry–Brønsted definition, an acid is a proton donor and a base is a proton acceptor [2]. According to the Lewis definition, acids are molecules or ions capable of coordinating with unshared electron pairs, and bases are molecules or ions having unshared electron pairs available for sharing with acids [3]. To be acidic in the Lewis sense, a molecule must be electron-deficient. This is the most general acid–base concept. All Lowry–Brønsted acids are Lewis acids but, in addition, the Lewis definition includes many other reagents such as boron trifluoride, aluminum chloride, etc.

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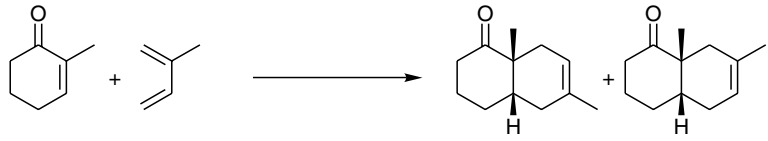
The discovery that Lewis acids can promote Diels–Alder reactions has become a powerful tool in synthetic organic chemistry. Yates and Eaton [4] first reported the remarkable acceleration of the reactions of anthracene with maleic anhydride, 1,4-benzoquinone and dimethyl fumarate catalyzed by aluminum chloride. The presence of the Lewis-acid catalyst allows the cycloadditions to be carried out under mild conditions, reactions with low reactive dienes and dienophiles are made possible, and the stereoselectivity, regioselectivity and site selectivity of the cycloaddition reaction can be modified [5]. Consequently, increasing attention has been given to these catalysts in order to develop new regio- and stereoselective synthetic routes based on the Diels–Alder reaction.

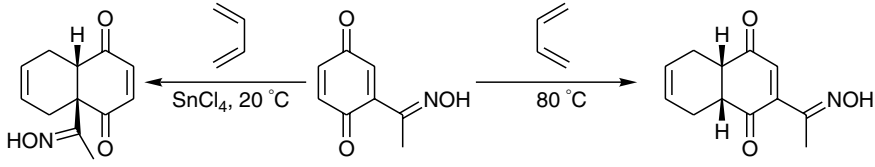
Examples of the effects of Lewis-acid catalysts on the selectivities are reported in Scheme 3.1.

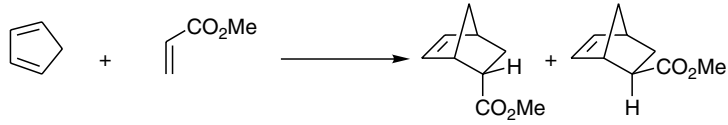
This Lewis acid ability of increasing both the reaction rate and the selectivity of the cycloaddition is surprising, since in other catalyzed reactions an increase in the reaction rate is accompanied by a decreased selectivity according to the reactivity–selectivity principle. This apparently contradictory behavior of the Lewis acids has been explained theoretically [6,7].

Many Lewis-acid catalysts have been studied and used in the Diels–Alder reactions, ranging from the more commonly used strong Lewis acids such as $AlCl_3$, $TiCl_4$, $SnCl_4$, $ZnCl_2$, $ZnBr_2$, etc., to the milder lanthanide complexes and to the chiral catalyst.



Reaction Conditions	*para*/*meta*	Yield (%)
150 °C, 142 h	65:35	20
$AlCl_3$, 25 °C, 17 h	97:3	97





Reaction Conditions	*endo*/*exo*
DCM, 0 °C, 67 h	92:8
DCM, $AlCl_3$, 0 °C, 1 h	98:2

Scheme 3.1

This chapter will mostly deal with the applications of the Lewis-acid-catalyzed Diels–Alder reaction to organic synthesis and the influence of Lewis acids on reactivity, stereoselectivity and regioselectivity of the cycloadditions.

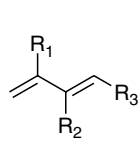
3.2 CARBON DIELS–ALDER REACTION

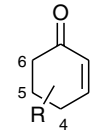
3.2.1 Cycloadditions of Cycloalkenones

Diels–Alder reactions of conjugated cycloalkenones provide a very important method for rapidly constructing complex polycyclic molecules. Since cycloalkenones are very poorly reactive dienophiles, acceleration by special physical and catalytic methods is required in order to avoid high reaction temperatures and long reaction times which often lead to low product yields [8].

A broad study of aluminum chloride-induced cycloadditions of cyclopentenones, cyclohexenones and cycloheptenones with 1,3-butadiene (**1**), isoprene

(**2**), (E)-piperylene (**3**) and 2,3-dimethyl-1,3-butadiene (**4**) (Figure 3.1) allowed all the reaction constraints to be determined, thus opening a straightforward route to the synthesis of hydrindanones, octalones and hydrobenzosuberones [9]. The diastereofacial selectivity in the catalyzed cycloadditions of 4-, 5- and 6-substituted 2-cyclohexenones **5** (Figure 3.1) has been extensively studied and the results (Table 3.1) have been interpreted in terms of a unifying stereoelectronic pathway and conformational considerations rather than a mere consideration of steric factors [10–12]. Diene–dienophile interaction, as shown for 4-alkylsubstituted 2-cyclohexenones in Scheme 3.2, occurs in such a way that (in the absence of steric interference) an axial diene approach antiparallel to the pseudo axial bond at neighboring C(4), which creates an incipient fused





1 $R_1 = R_2 = R_3 = H$

2 $R_1 = Me$, $R_2 = R_3 = H$

3 $R_1 = R_2 = H$, $R_3 = Me$

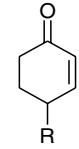
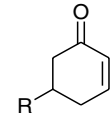
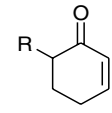
4 $R_1 = R_2 = Me$, $R_3 = H$

5 R = Me, *i*-Pr, *t*-Bu

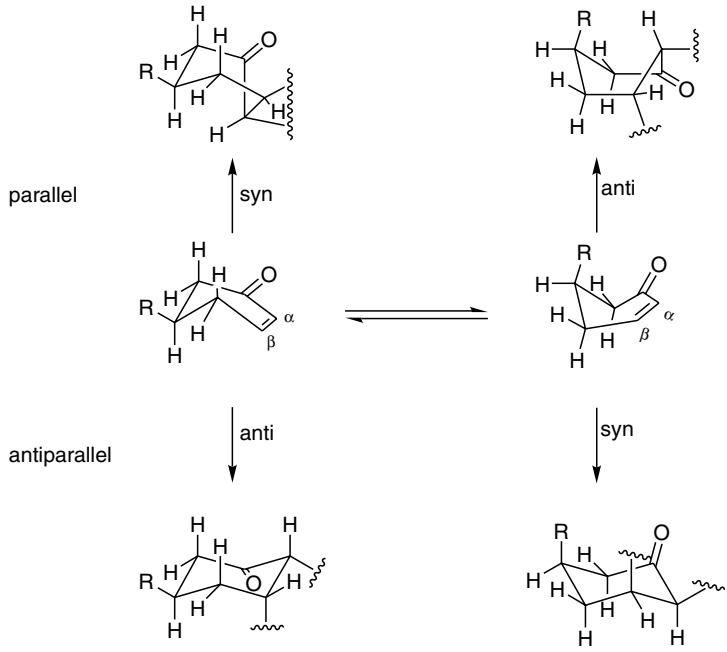
Figure 3.1

DropBooks

Table 3.1 Facialselectivity[a] in the aluminium chloride catalyzed Diels–Alder reactions of 4-, 5-and 6-substituted 2-cyclohexenones **5** with dienes **1**–**3**

Diene	R	Me	*i*-Pr	*t*-Bu	Dienophile
1		55	67	100	
2		90	91	100	
3		49	61	100	
1		96	92	97	
2		97	92	91	
3		96	98	97	
1					
2		35			
3		33			

[a] Expressed as % of *anti* Diels–Alder adducts.



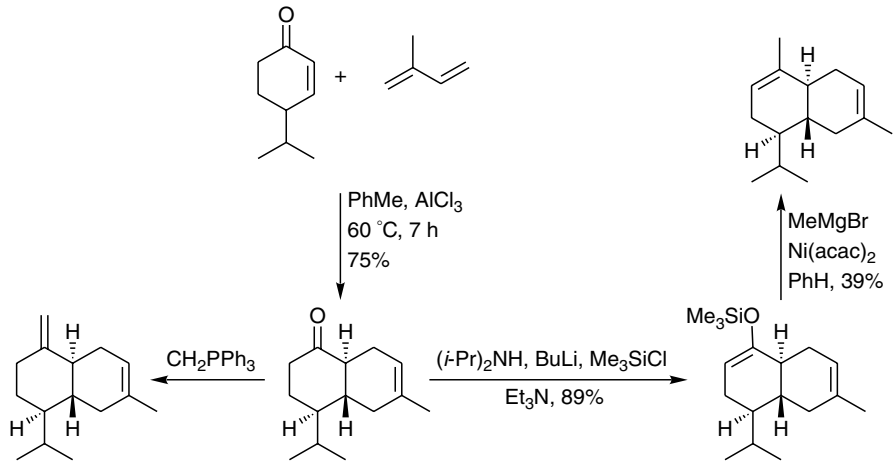
Scheme 3.2

cyclohexenone in half-chair conformation, is preferred over a parallel approach which produces the same ring in initial half-boat form. The adducts coming from Lewis-acid-catalyzed Diels–Alder reaction of 2-unsubstituted 2-cycloalkenones can epimerize at C-2 and therefore the *trans* adduct is sometimes the main reaction product.

Highly *anti*-diastereofacial selective cycloaddition of isoprene **(2)** with 4-isopropyl-2-cyclohexenone allowed a short regiocontrolled and stereocontrolled synthesis [13] of β-cadinene and (γ_2-cadinene, Scheme 3.3). High *anti*-diastereofacial selectivity also occurs in the Diels–Alder reaction of optically active cyclohexenones **6–9** (Figure 3.2), readily available from the chiral pool, with open chain dienes [14–16]. Their cycloadducts are valuable intermediates in the synthesis of optically active sesquiterpenes in view of the easy conversion of the gem-dimethylcyclopropane and gem-dimethylcyclobutane in a variety of substituents.

Bicyclic [6.4.0]dodecane systems have been prepared [17] by catalyzed and photochemical intermolecular cycloaddition of the cyclooct-2-en-1-ones **10** and 1,3-butadiene (**1**) and by catalyzed intramolecular cycloaddition of trienone **11** (Scheme 3.4).

A strong dependence of the diastereofacial selectivity [18] on the substituents has been observed in the catalyzed cycloadditions of acyclic dienes with



Scheme 3.3

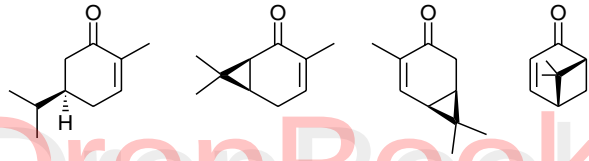


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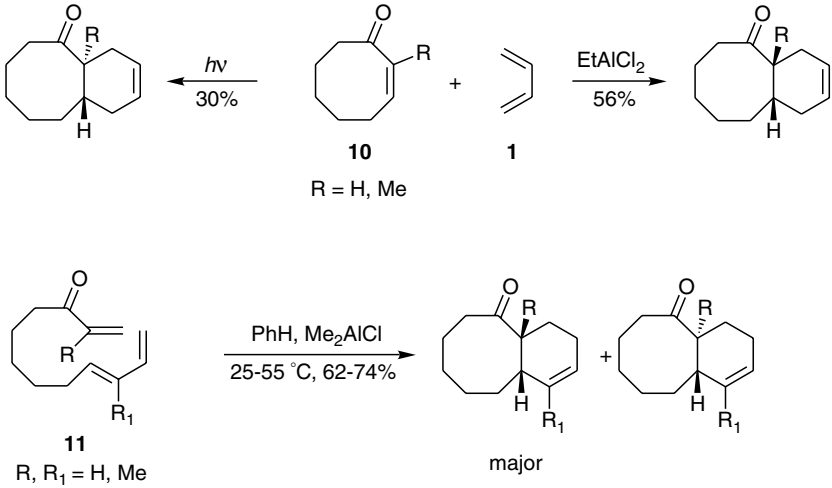
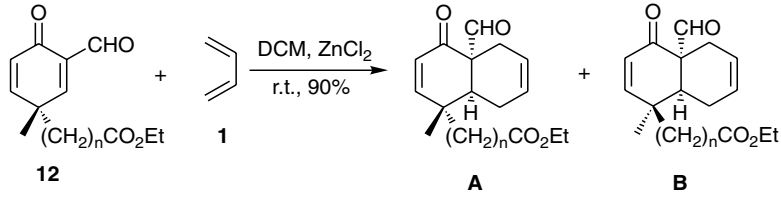
Figure 3.2



Scheme 3.4

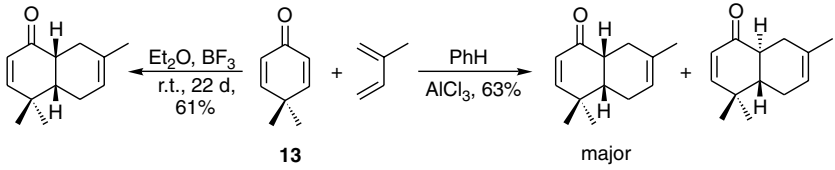
4,4-disubstituted dienones **12** (Scheme 3.5). Whereas the cycloadditions of 1,3-butadiene (**1**) with dienones **12b** and **12c** showed a clear preference for the *anti*-diastereoselectivity (*anti* with respect to the C-4 ester group), a reversal *syn*-diastereofacial selectivity was observed in the cycloaddition of dienone **12a**. Similar results were observed in the cycloaddition with (E)-piperylene.



12	n	A/B
a	0	0:100
b	1	63:37
c	2	84:16

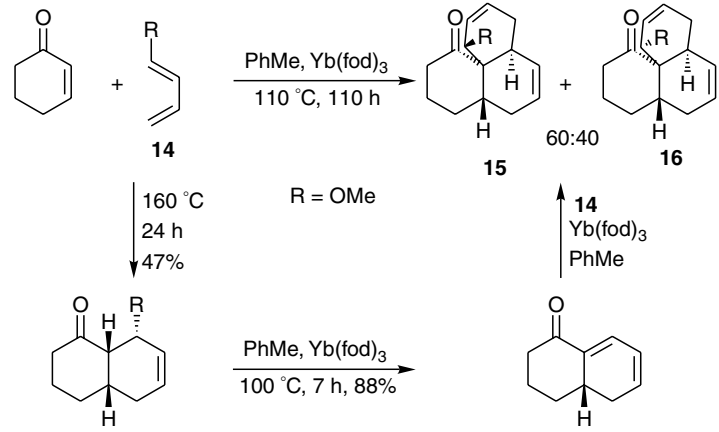
Scheme 3.5

The presence of two substituents at C-4 also strongly influences the regioselectivity as shown in the cycloaddition of dienone **13** with isoprene (**2**) (Equation 3.1). In violation of the *para*-rule for Diels–Alder reaction, only *meta*-adduct was obtained [19,20].



(3.1)

The presence of the catalyst can also favor multiple Diels–Alder reactions of cycloalkenones. Two typical examples are reported in Schemes 3.6 and 3.7. When (E)-1-methoxy-1,3-butadiene **(14)** interacted with 2-cyclohexenone in the presence of $Yb(fod)_3$ catalyst, a multiple Diels–Alder reaction occurred [21] and afforded a 1:1.5 mixture of the two tricyclic ketones **15** and **16** (Scheme 3.6). The sequence of events leading to the products includes the elimination of methanol from the primary cycloadduct to afford a bicyclic dienone that underwent a second cycloaddition. Similarly, 4-acetoxy-2-cyclopenten-1-one **(17)** (Scheme 3.7) has been shown to behave as a conjunctive reagent for a one-pot multiple Diels–Alder reaction with a variety of dienes under $AlCl_3$ catalysis, providing a mild and convenient methodology to synthesize hydrofluorenones [22]. The role of the Lewis acid is crucial to facilitate the elimination of acetic acid from the cycloadducts. The results of the reaction of **17** with diene



Scheme 3.6

4 are reported in Scheme 3.7. 4-Acetoxy-2-cyclopenten-1-one **(17)** behaves like a synthetic equivalent of the cyclopentadienone [23].

In a practical sense the instability of the alkoxy-, acyloxy-and silyloxy-substituted cycloadducts under Lewis-acid-catalyzed conditions may sometimes be a

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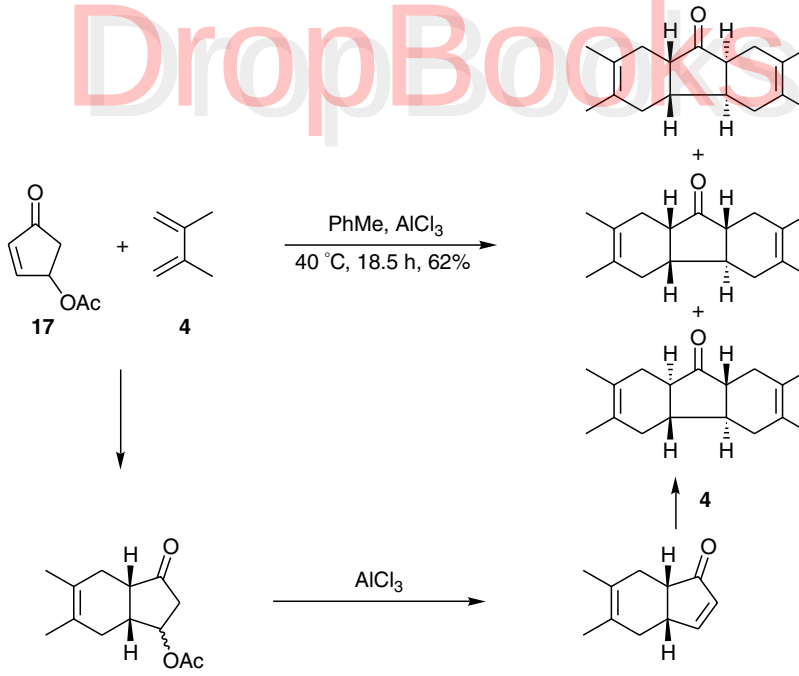
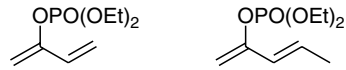


Scheme 3.7

serious problem in the Diels–Alder reaction, as well as in further transformations of the adducts. Diethylphosphoryloxybutadienes such as **19** and **20** (Figure 3.3), and the cycloadducts derived from them, are significantly stable, thus retaining a high degree of synthetic usefulness [24].

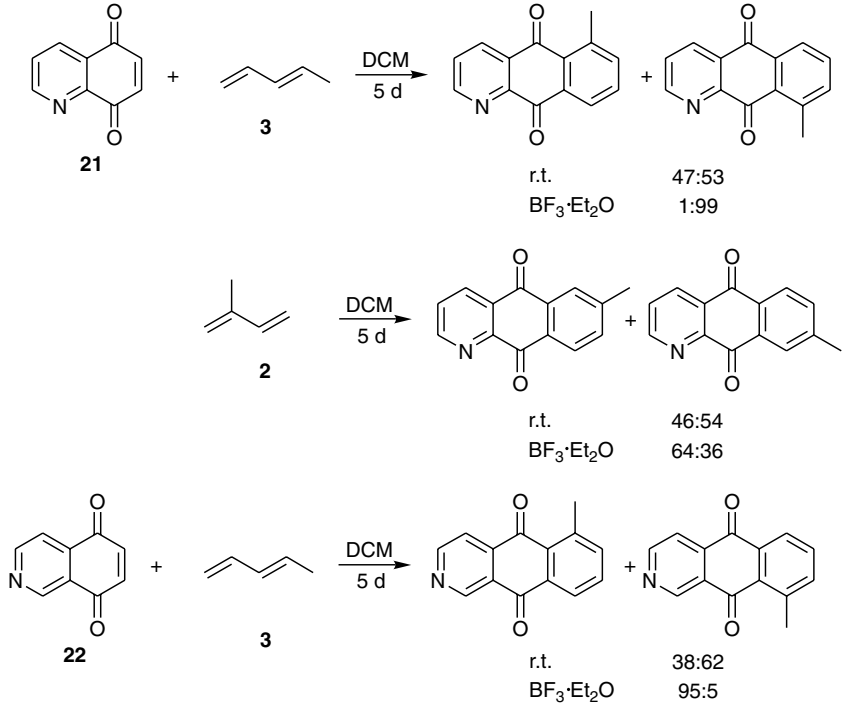


19 **20**

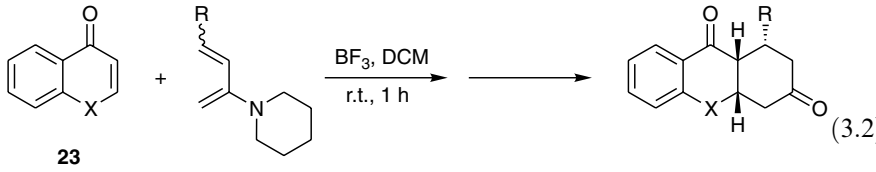
Figure 3.3

3.2.2 Heterocyclic Dienophiles

Strong effects of the catalyst on the regioselectivity have been observed in the cycloadditions of a variety of heterocyclic dienophiles. Some results of the BF_3-catalyzed reactions of quinoline-5,8-dione **(21)** and isoquinoline-5,8-dione **(22)** with isoprene **(2)** and (E)-piperylene **(3)** [25], and of the cycloadditions of 4-quinolones (**23a**, **23b**) as well as 4-benzothiopyranone **(23c)** with 2-piperidinobutadienes, are reported [26] in Scheme 3.8 and Equation 3.2. The most marked



Scheme 3.8



(3.2)

23

a X = NCO_2Et R = *i*-Pr, *t*-Bu, Cy
b X = NCbz
c X = S

influence was observed in the reaction of **21** with (E)-piperylene. This has been rationalized by considering the secondary orbital interactions of piperylene's HOMO with the LUMOs of catalyst–dienophile complexes.

Similarly a marked increase of regioselectivity has been shown in the catalyzed Diels–Alder reactions of the chiral bicyclic lactame **24** (Scheme 3.9) with a variety of dienes [27] (isoprene, mircene, (E,E)-1,4-dimethylbutadiene, 2,3-dimethylbutadiene, 2-siloxybutadiene). The catalyzed reactions were more regioselective and totally *endo-anti*-diastereoselective (*anti* with respect to the bridgehead methyl group). The results of the cycloadditions with isoprene and mircene are reported in Scheme 3.9. The cycloadducts have then been used to provide interesting fused carbocycles [28] with high enantiomeric purity as shown in Scheme 3.10.

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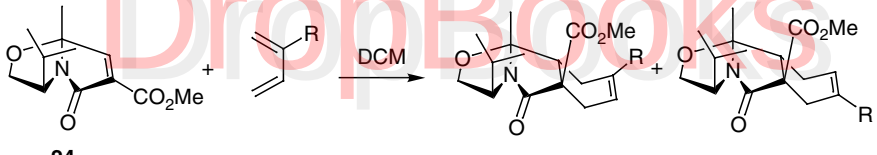
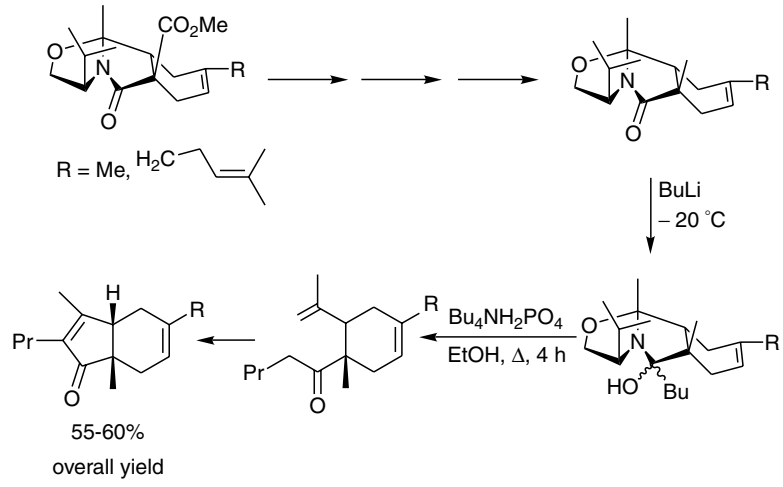


24 **A** **B**

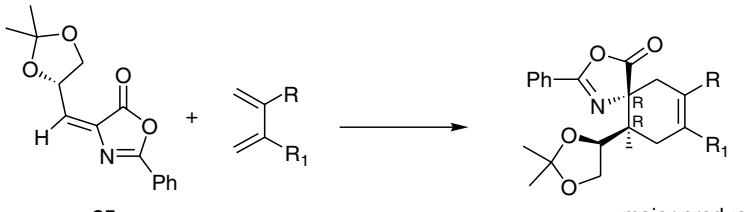
R	Cat	T (°C)	t (h)	**A**/**B**	Yield (%)
Me	-	60	24	2	74
Me	$ZnCl_2$	0	4	25	71
H_2C	-	60	18	2.3	75
H_2C	$ZnCl_2$	0	36	15.2	66

Scheme 3.9

(E)-Azlactones are among the most important precursors of α-amino acids [29], but the less stable (E)-isomer easily isomerizes to the (Z)-isomer affording, as a consequence, in the Diels–Alder reaction complex mixtures of cycloadducts. The use of some heterogeneous catalysts (SiO_2–Et_2AlCl, SiO_2–$TiCl_4$, SiO_2–$ZnCl_2$) reduces the E/Z isomerization [30] and allows the selectivity of the Diels–Alder reaction to be improved, as shown for the chiral azlactone **25** (Equation 3.3). The best control has been obtained with SiO_2–$ZnCl_2$. Equation



Scheme 3.10



(3.3)

R = Me, R_1 = H	20 °C, 24 h	27%
	SiO_2-$ZnCl_2$	81%
R = R_1 = Me	20 °C, 24 h	78%
	SiO_2-$ZnCl_2$	94%

3.3 reports the percentages of the major component of the reaction mixtures obtained in the cycloadditions with isoprene **(2)** and 2,3-dimethylbutadiene **(4)** under thermal and SiO_2–$ZnCl_2$ catalyzed conditions.

Chiral tricyclic compounds have been prepared by thermal and $Eu(fod)_3$-catalyzed cycloadditions of furanosidic α,β-unsaturated aldehydes **26–29** (Figure 3.4) with cyclopentadiene **(18)** [31]. The diastereofacial selectivity depends markedly on the stereochemistry of the anomeric benzyloxy and methoxy groups.

3.2.3 Rare Earth Metals and Scandium Triflates

Rare earth metals and scandium trifluoromethanesulfonates (lanthanide and scandium triflates) are strong Lewis acids that are quite effective as catalysts in

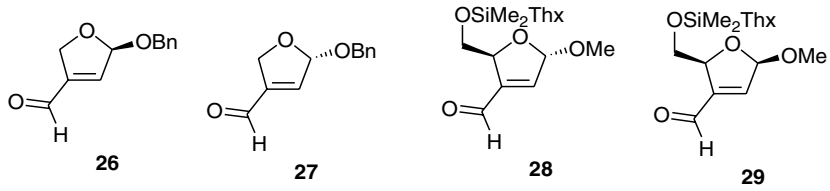


Figure 3.4

the cycloadditions of carbonyl-containing dienophiles. These compounds were expected to act as strong Lewis acids because of their hard character and the electron-withdrawing trifluoromethanesulfonyl group, and to have a strong affinity toward carbonyl oxygen. These catalysts, such as $Yb(OTf)_3$, have been used successfully [32] in the reactions of cyclopentadiene **(18)** with acyclic aldehydes and ketones, quinones and cycloalkenones, and have also been used in the inverse electron-demand cycloadditions. It must be emphasized that a catalytic amount of catalyst is enough to accelerate the reactions and that the catalyst can be easily recovered and reused.

Scandium triflate [33] is a more active catalyst than the lanthanide triflates and the cycloadditions can also be carried out in aqueous media (Chapter 4). The catalyst is easily recovered from the aqueous layer after the reaction is completed, and can be reused. Some of the cycloadditions carried out in DCM and catalyzed by $Sc(OTf)_3$ are summarized in Table 3.2.

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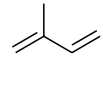
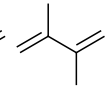
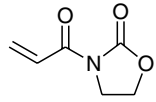
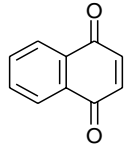
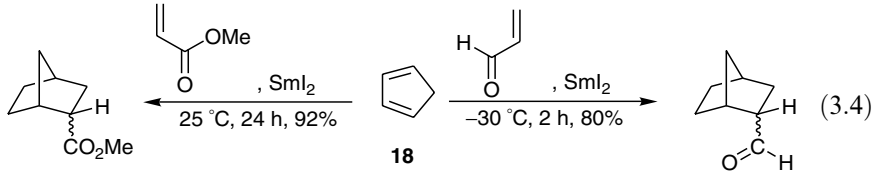
Table 3.2 Reaction yield (%) of Diels–Alder reactions catalyzed by $Sc(OTf)_3$ (DCM, 0 °C, 10 mol % cat)

Dienophile				
	90	86	95	89
	91	88	96	83
		92	83	62

Whereas lanthanide triflates are strong Lewis acids, lanthanide complexes such as $Yb(fod)_3$ and $Eu(fod)_3$ are mild catalysts that can be used when the cycloaddition involves acid-sensitive reagents and/or cycloadducts [34].

Diiodosamarium [35] is a mild catalyst that can be used with success as an alternative to $Eu(fod)_3$ or $Yb(fod)_3$ in both all carbons and *hetero*-Diels–Alder reactions (Equations 3.4 and 3.5).



(3.4)

(3.5)

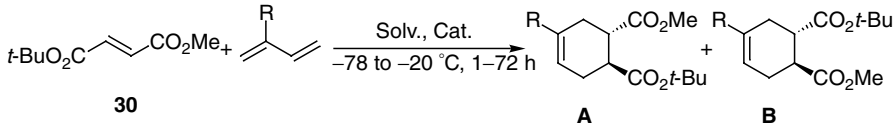
R = Ph, Ph-CH=CH-, 2-Fu

3.2.4 Bulky Lewis Acids

Regio- and stereochemical control in the catalyzed Diels–Alder reactions also depends on the chelating and non-chelating ability of Lewis-acid catalysts. These two types of catalysts can lead to an opposite diastereoselectivity depending either on the ability of Lewis-acidic reagents to form intermediate chelates that are attacked stereoselectively from the less hindered site (chelation control) or on the reagent incapability of chelation (non-chelation control), the stereoselectivity being governed by electronic and/or steric factors [36]. Bulky methylaluminum-bis-(4-methyl-2,6-di-*tert*-butylphenoxide) (MAD) and methylaluminum-bis-(4-bromo-2,6-di-*tert*-butylphenoxide) (MABR) are examples of efficient non-chelating Lewis acids and show a remarkably high regio- and stereochemical control, as shown in the cycloaddition of unsymmetrical fumarate [37] **30** with 2-substituted 1,3-butadienes (Scheme 3.11) and of acrylate [36] **31** with cyclopentadiene **(18)** (Scheme 3.12). The stereoselectivity in these cases is controlled by the incapability of chelation of the bulky catalysts.

3.2.5 Heterocyclic Dienes

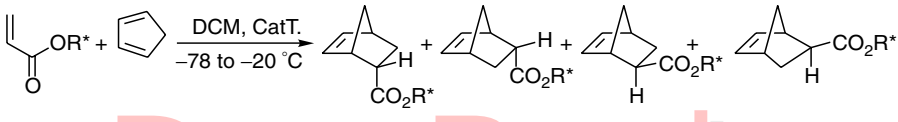
Highly functionalized benzenes and naphthalenes have been prepared by cycloaddition of zirconacyclopentadiene **32** and its benzoderivative **33** [38] with



30 A B

R	Catalyst	Solvent	A/B
Me	–	PhMe	56:44
	Et_2AlCl	DCM	44:56
	MAD	DCM	14:86
	MAD	PhMe	20:80
$OSiMe_3$	–	PhMe	48:52
	Et_2AlCl	DCM	44:56
	MAD	DCM	1:99
	MAD	PhMe	17:83

Scheme 3.11



31 18 A B C

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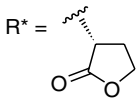
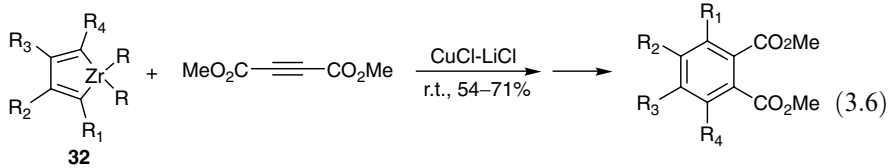
R* =



Cat. (equiv.)	*endo/exo*	A/B	Yield (%)
$TiCl_4$ (1)	97:3	97:3	83
$SnCl_4$ (2)	97:3	97:3	97
$EtAlCl_2$ (2)	99:1	86:14	97
MAD (2)	95:5	5:95	96
MABR (2)	89:11	5:95	97

Scheme 3.12

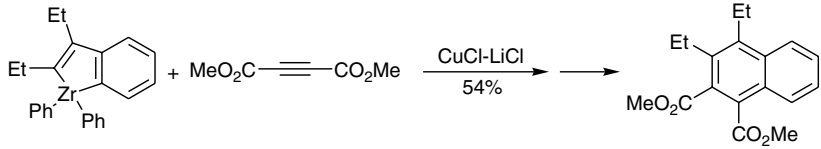
alkynes [39] in the presence of a stoichiometric amount of CuCl/LiCl. Equations 3.6 and 3.7 report the results of the cycloadditions with DMAD. In the absence of copper salts, the diene was unreactive.



(3.6)

32

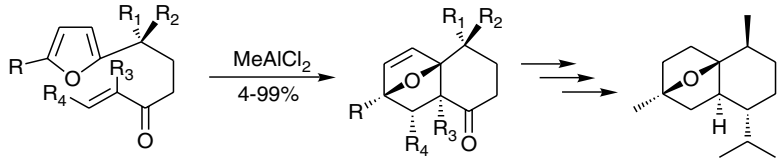
R = Ph; R_1, R_2, R_3, R_4 = Me, Et, Bu, Ph, $SiMe_3$



(3.7)

33

Intramolecular cycloadditions of furans are a useful method for creating an oxygenated cyclohexane ring in rigid cycloadducts. Thus, a $MeAlCl_2$-catalyzed intramolecular reaction [40] of compounds **34** leads stereoselectively to tricyclic cycloadducts (Equation 3.8). The reaction yield is strongly dependent on the quantity of the catalyst and the type of substituent at the olefinic double bond. Cycloadduct **35** ($R = R_2 = Me$, $R_1 = R_3 = R_4 = H$) was then converted [40b] into 1,4-epoxycadinane **(36)**.

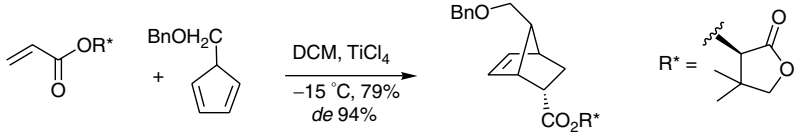


(3.8)

34 **35** **36**

R, R_1, R_2, R_3, R_4 = H, Me

The catalyst played an important role in the asymmetric synthesis of Corey lactone based on high diastereofacial selective Diels–Alder reaction between chiral acrylate **37** and 5-benzyloxymethylcyclopentadiene [41] (Equation 3.9). The cycloadduct **38** was then converted into chiral Corey lactone [42] by a three-step procedure.



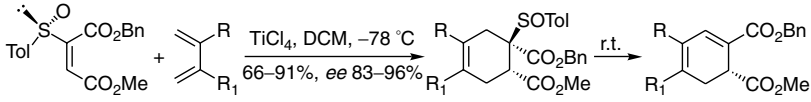
(3.9)

37 **38**

3.2.6 Sulfinyl Group Containing Dienes and Dienophiles

It has been shown that the sulfinyl group present as chiral auxiliary either in dienophiles or in dienes is very useful for controlling the enantio- and diastereofacial selectivity in the asymmetric Diels–Alder reaction [43]. A wide variety of enantiomerically pure cyclohexadienedicarboxylates has been produced by cycloaddition of the sulfinylmaleate **39** with several dienes under catalyzed

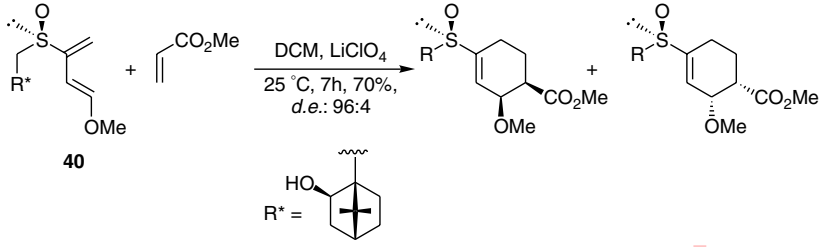
conditions (Equation 3.10). The cycloadduct then eliminates spontaneously the sulfinyl group at room temperature [44].



(3.10)

39 R, R_1 = H, Me, OMe

Sulfinyldiene **40** reacts, regio- and stereoselectively, with methylacrylate in the presence of a catalyst, affording carbomethoxycyclohexene derivatives [45]. Among the catalysts examined, the best was lithium perchlorate used as a suspension in DCM; it gave only *endo* isomers in 70% yield in a 96:4 d.e. ratio (Equation 3.11).

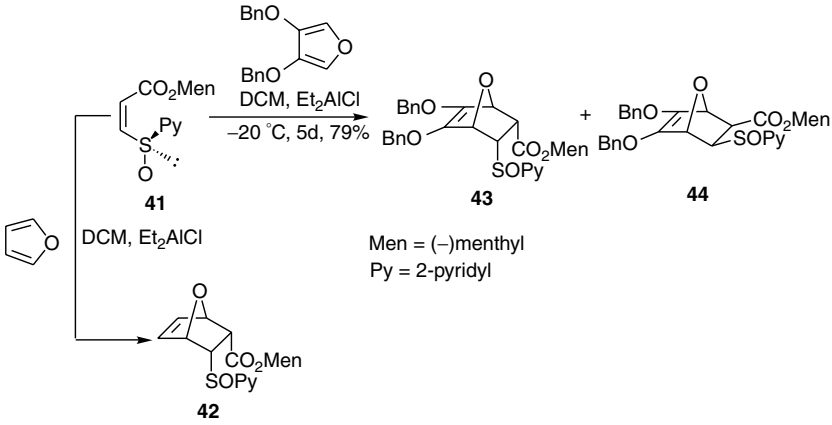


(3.11)

40

DropBooks

Sulfinylacrylate **41** has been successfully used in the enantioselective synthesis of pseudo-sugar [46, 47]. Cycloaddition of (S)-3-(2-pyridylsulfinylacrylate) **(41)** with furan and 3,4-dibenzyloxyfuran under Et_2AlCl catalysis afforded cycloadducts **42**, **43** and **44** (Equation 3.12) which were converted into pseudo-mannopyranoses **45**, **46** and **47** (Figure 3.5).



(3.12)

41 **43** **44** **42**

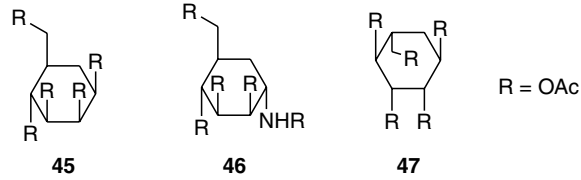


Figure 3.5

3.2.7 Transition-Metal-Based Catalysts

The most commonly used traditional Lewis acids are halides of aluminum, boron, titanium, zinc, tin, and copper. However, there are also more complex Lewis-acids that are quite effective catalysts that can be easily modified for carring out enantioselective processes, by incorporating chiral ligands. These can overcome some limitations associated with the use of classical Lewis acids [47].

Ferrocenium hexafluorophosphate **(48)** and catecholboronbromide **(49)** (Figure 3.6) are efficient catalysts that have been tested in the cycloadditions of cyclic and acyclic dienes with a variety of dienophiles [48]. Catalyst **48** is less active than **49**, but is less corrosive.

Transition-metal-based Lewis acids such as molybdenum and tungsten nitrosyl complexes have been found to be active catalysts [49]. The ruthenium-based catalyst **50** (Figure 3.6) is very effective for cycloadditions with aldehyde- and ketone-bearing dienophiles but is ineffective for α,β-unsaturated esters [50]. It can be handled without special precautions since it is stable in air, does not require dry solvents and does not cause polymerization of the substrates. Nitromethane was the most convenient organic solvent; the reaction can also be carried out in water.

The cyclopentadienyl triflate complexes of zirconium and titanium **51** and **52** (Figure 3.7) are also active catalysts [51]. Their activity has been tested in a wide variety of dienes and dienophiles. It is noteworthy that even at low catalyst loadings, rate accelerations between 10^3 and $> 10^5$ times have been observed. No special precautions were taken to dry the solvents or the substrates, in contrast with the traditional Lewis acids which require either predried solvents or high catalyst loadings.

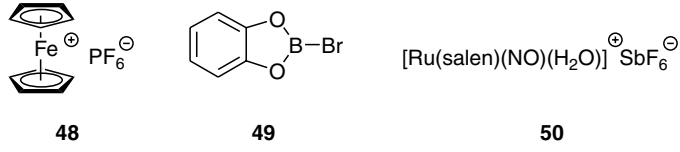


Figure 3.6

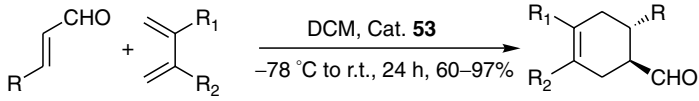
$[Zr(Cp)_2(CF_3SO_3)_2THF]$ **51**

$[Ti(Cp)_2(CF_3SO_3)_2]$ **52**

Figure 3.7

3.2.8 Heterogeneous Catalysis

Supported Lewis acids are an interesting class of catalysts because of their operational simplicity, filterability and reusability. The polymer-bound iron Lewis-acid **53** (Figure 3.8) has been found [52] to be active in the cycloadditions of α,β-unsaturated aldehydes with several dienes. It has been prepared from (η^5-vinylcyclopentadienyl)dicarbonylmethyliron which was copolymerized with divinylbenzene and then treated with trimethylsilyltriflate followed by THF. Some results of the Diels–Alder reactions of acrolein and crotonaldehyde with isoprene **(2)** and 2,3-dimethylbutadiene **(4)** are summarized in Equation 3.13.

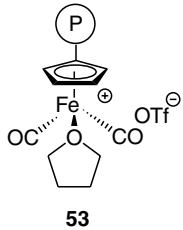


(3.13)

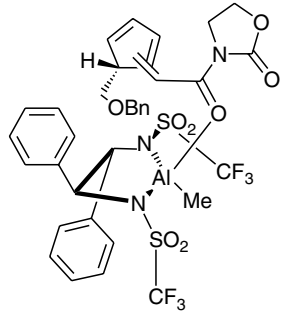
R = H, Me R_1, R_2 = H, Me

DropBooks

Several aluminum- and titanium-based compounds have been supported on silica and alumina [53]. Although silica and alumina themselves catalyze cycloaddition reactions, their catalytic activity is greatly increased when they complex a Lewis acid. Some of these catalysts are among the most active described to date for heterogeneous catalysis of the Diels–Alder reactions of carbonyl-containing dienophiles. The SiO_2–Et_2AlCl catalyst is the most efficient and can be



53



55

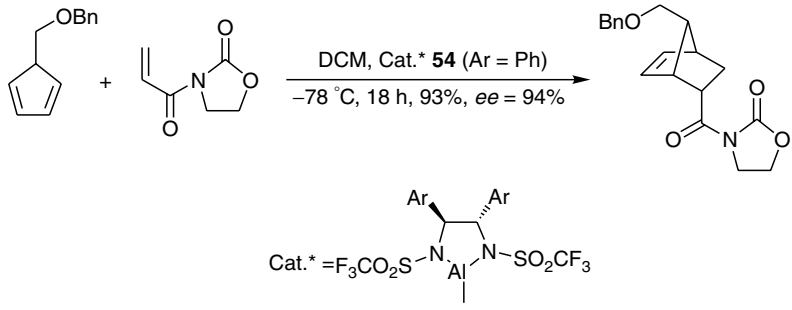
Figure 3.8

recovered and stored without a great loss of catalytic activity even if kept in the open air for a month. Other examples have been reported in Section 3.2.2.

3.2.9 Chiral Catalysts

Asymmetric induction in the intermolecular Diels–Alder cycloaddition reactions can be achieved with chirally modified dienes and dienophiles as well as with chiral Lewis-acid catalysts [54–56].

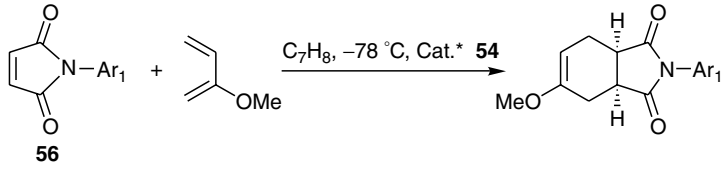
Aluminum-based catalyst (S,S)-diazaaluminolidine **54** promoted the cycloaddition [57] between 5-(benzyloxymethyl)-1,3-cyclopentadiene and 3-acryloyl-1, 3-oxazolidin-2-one, leading to the cycloadduct in high yield and high enantiomeric excess (94%) (Equation 3.14).



(3.14)

54

The transition state assembly **55** (Figure 3.8), that rationalizes the stereochemistry of the cycloadduct, is consistent with the structure of the chiral catalyst determined by an X-ray diffraction study. Interestingly it has been shown [58] that in the cycloadditions of maleimides **56** with 2-methoxy-1,3-butadiene, the enantioselection depends on the bulkiness of Ar and Ar_1 groups of catalyst **54** and dienophile **56**, respectively (Scheme 3.13). The importance of the bulky Ar_1



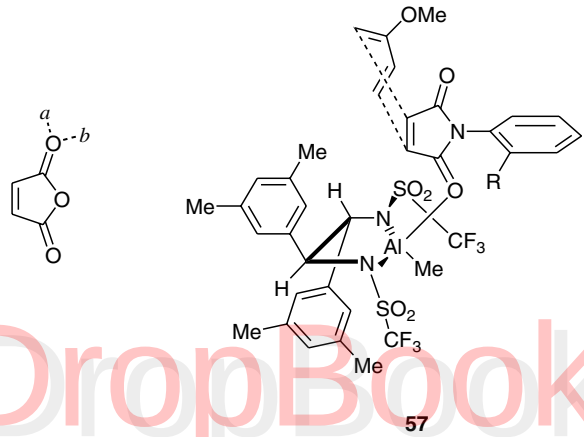
56

Ar (**54**)	Ar_1 (**56**)	(*ee* %)
Ph	Ph	35
Ph	*o*-MeC_6H_4	58
Ph	*o*-*t*-Bu-C_6H_4	52

Ar (**54**)	Ar_1 (**56**)	(*ee* %)
3,5-$Me_2C_6H_3$	Ph	62
3,5-$Me_2C_6H_3$	*o*-MeC_6H_4	93
3,5-$Me_2C_6H_3$	*o*-*t*-Bu-C_6H_4	95

Scheme 3.13

groups at the nitrogen atom of **56** is demonstrated by the fact that the cycloaddition of the same diene (2-methoxy-1,3-butadiene) with maleic anhydride, catalyzed by **54** (Ar = Ph), produces a racemic adduct. This phenomenon can be readily explained if the coordination of the catalyst to maleic anhydride occurs at carbonyl oxygen lone pair *b* rather than at lone pair *a*. Coordination at lone pair *b* places the dienophilic double bond so far from the chiral catalyst that no enantioselection can be expected. In the case of maleimides, coordination of the catalyst to lone pair *b* is effectively blocked by the bulky Ar_1 group. The transition state assembly that leads to the observed stereochemistry of the cycloadduct is depicted in formula **57** (Figure 3.9).



57

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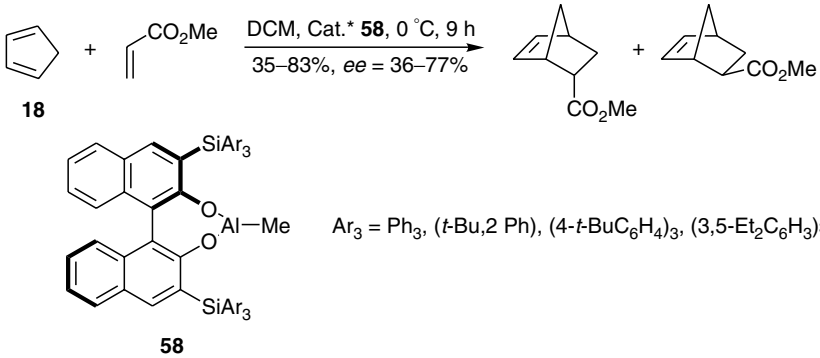
Figure 3.9

In contrast, modest enantioselection has been observed in the asymmetric Diels–Alder reaction between cyclopentadiene **(18)** with methylacrylate and methylpropiolate catalyzed by chiral organoaluminum reagents **58** [59] (Equation 3.15) prepared from trimethylaluminum and (R)-(+)-3,3′-bis(triphenylsilyl)-1,1′-bi-2-naphthol [60]. The reaction was highly *endo*-diastereoselective.



Ar_3 = Ph_3, (*t*-Bu,2 Ph), (4-*t*-$BuC_6H_4)_3$, (3,5-$Et_2C_6H_3)_3$ (3.15)

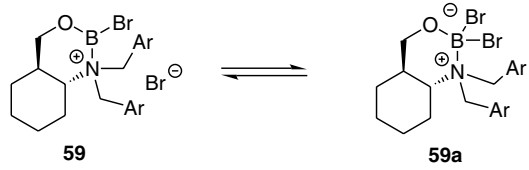
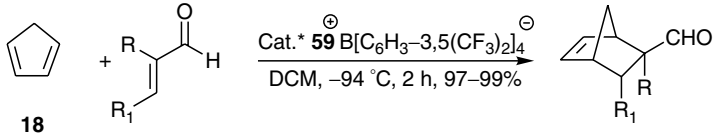
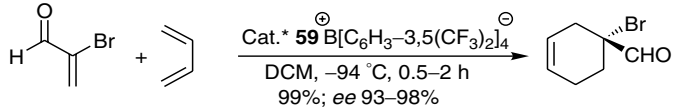


Figure 3.10

Cationic oxazaborinane **59** (Figure 3.10) is a chiral super-Lewis-acidic catalyst recently described by Corey and coworkers [61]. The catalyst is in equilibrium with **59a** and the oxazaborinane system **59** ⇆ **59a** is unstable and undergoes gradual decomposition at temperatures above −60 °C. A more active catalyst system is the tetraarylborate salt $\mathbf{59}^{+}B[C_6H_3-3,5-(CF_3)_2]_4^{-}$ which allows the cycloadditions of cyclopentadiene **(18)** and α,β-unsaturated aldehydes to occur with a high level of stereoselectivity and enantioselectivity (Equations 3.16 and 3.17).

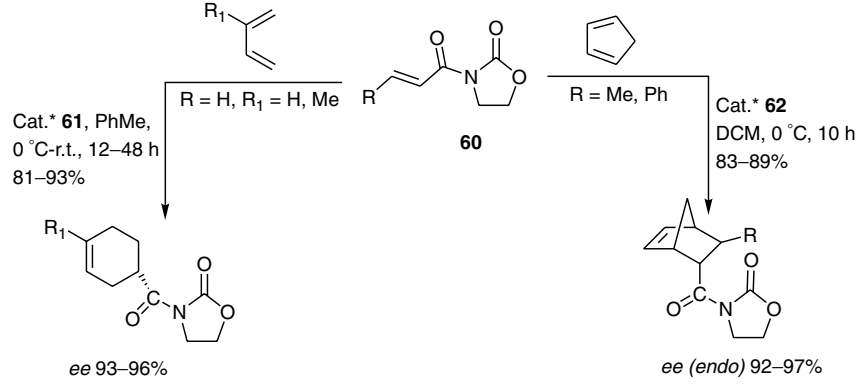


(3.16)

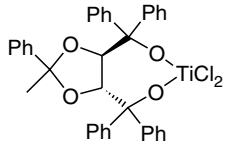


(3.17)

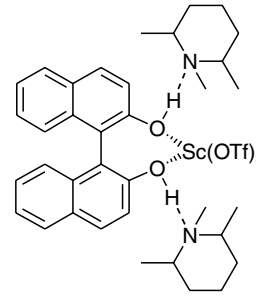
Chiral titanium- and scandium-based catalysts (**61** and **62**, Figure 3.11) were used to accelerate the cycloadditions of acyl-1,3-oxazolidin-2-ones **60** (Scheme 3.14) with butadiene, isoprene and cyclopentadiene. The cycloadditions



Scheme 3.14



61



62

Figure 3.11

occurred with an excellent enantiomeric excess and are a valuable method for preparing chiral cyclohexene and norbornene carboxylic acid derivatives [62,63] (Scheme 3.14). The high level of enantioselection is explained considering that the complexation of dienophile occurs either as depicted in **63** or as in **64** (Figure 3.12), the *re-face* of dienophile being always that preferentially attacked. Titanium-based catalyst **61** was prepared (Equation 3.18) by the alkoxy exchange between dichloroisopropoxytitanium(IV) and a chiral 1,4-diol derived from (2R, 3R)-tartrate in the presence of molecular sieves MS4A,

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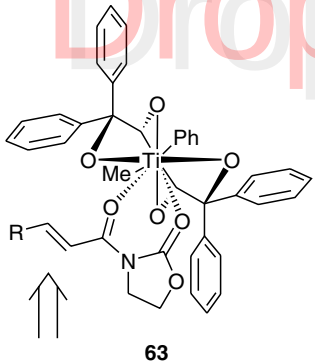

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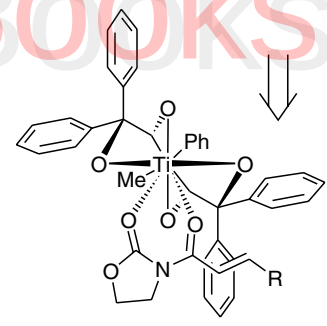
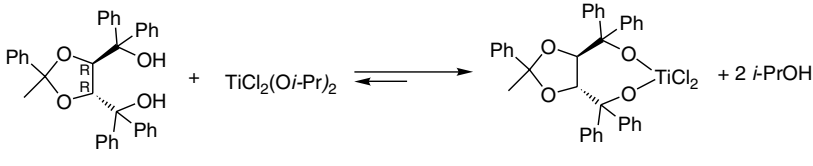


64

Figure 3.12

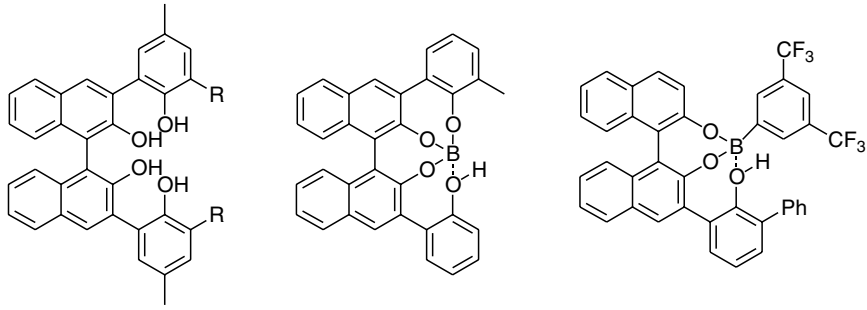


(3.18)

61

and scandium-based catalyst **62** was prepared from scandium triflate, R-(+)-1,1′-bi-2-naphthol[(R)-BINOL] and a tertiary amine. The enantioselection depends strongly on the nature of the amine: the best results were obtained with *cis*-1,2,6-trimethylpiperidine.

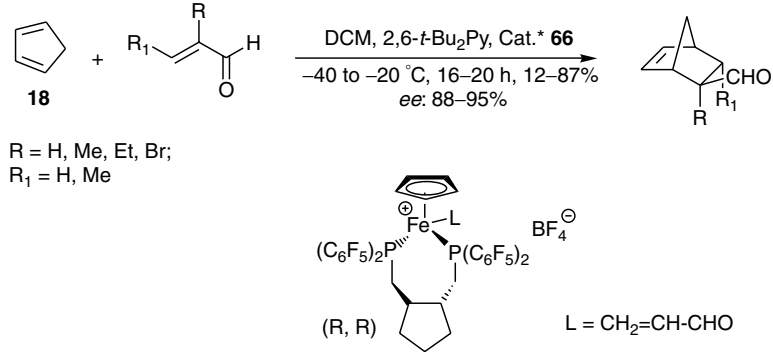
Binaphthol-derived titanium complexes [64], prepared from chiral ligands **65** (Figure 3.13), also performed very well in the cycloadditions of conjugated aldehydes with cyclic and acyclic dienes. Judging from the absolute configurations of *endo* and *exo* adducts, this catalyst should cover the *re-face* of carbonyl on its *anti*-coordination to *s-trans* α,β-unsaturated aldehydes, and hence dienes should approach selectively from the *si-face*.



65 **68** **69**

Figure 3.13

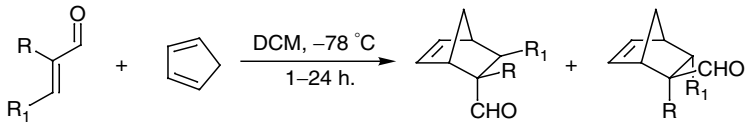
When the iron-based catalyst **66** was used, a high level of enantiomeric excess in the cycloadditions between cyclopentadiene **(18)** and α,β-unsaturated aldehydes [65] was observed. The cycloadditions were carried out in the presence of 2,6-di-t-butylpyridine (Scheme 3.15) which was added to scavenge residual acid impurities.



66

Scheme 3.15

Table 3.3 Diels–Alder reactions of α,β-unsaturated aldehydes (**67**) with cyclopentadiene (**18**) catalyzed by (R)-BLA **68** and (R)-BLA **69**



67 **18** *endo* *exo*

	(R)-BLA **68**			(R)-BLA **69**		
Dienophile	Yield (%)	*endo/exo*	*ee* (%)	Yield (%)	*endo/exo*	*ee* (%)
$R = R_1 = H$	91	9:91	40 (R)	84	3:97	95 (S)
$R = Br, R_1 = H$	>99	99:1	99 (S)	99	90:10	99 (R)
$R = Me, R_1 = H$	>99	99:1	99 (R)			
$R = Et, R_1 = H$	>99	97:3	92			
$R = H, R_1 = Me$	12	11:89	36 (R)	94	10:90	95 (S)
$R = R_1 = Me$	99	99:1	98	90	98:2	96
$R = H, R_1 = Et$				73	9:91	98
$R = H, R_1 = CO_2Et$				91	2:98	95 (S)

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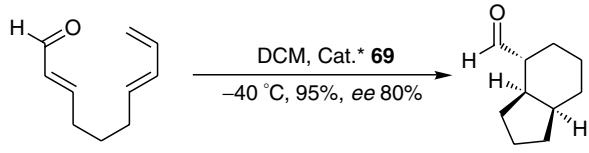
Brønsted acid-assisted chiral Lewis acids (BLA) are an interesting class of catalysts which efficiently induce asymmetry in the Diels–Alder reaction through the combination of intramolecular hydrogen bonding and attractive π–π donor–acceptor interactions between the dienophile and the chiral ligand in the transition state by hydroxy aromatic groups present in chiral Lewis acids [66]. The geometry of the catalyst is of great importance for a high level of asymmetric induction. Yamamoto and coworkers [67] have synthesized several BLAs by using different chiral ligands and various boron compounds. Examples are (R)-BLA **68** and (R)-BLA **69** (Figure 3.13). Table 3.3 summarizes the results of the Diels–Alder reactions of α,β-unsaturated aldehydes **67** and cyclopentadiene **(18)** catalyzed by these catalysts. The best catalyst was **69** because it activates the Diels–Alder reactions of both α- and β-substituted enals and shows an absolute stereopreference opposite to that found by using **68**. This means that the presence of the electron-withdrawing trifluoromethyl groups affects the asymmetric induction of the catalyst. The efficiency of these catalysts was also tested in intramolecular cycloadditions (Equation 3.19). Only *endo* adduct **71** with 80% *ee* and 95% yield was obtained from trienal **70**. This result was much better than the 74% yield, 46% *ee*, *exo/endo* = 1:99 previously given by a chiral acyloxyborane-catalyzed reaction [68].



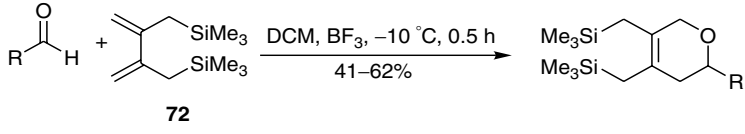
70 **71** (3.19)

3.3 *HETERO*-DIELS–ALDER REACTION

3.3.1 Normal Diels–Alder Reactions. Synthesis of Pyrones and Thiopyrans

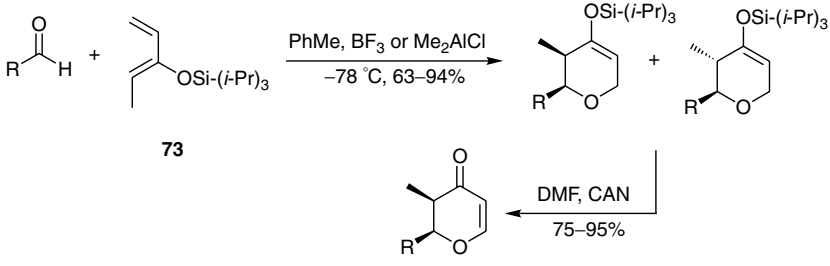
Hetero-Diels–Alder reactions provide one of the most convenient tools for synthesizing heterocyclic compounds [69,70].

Dihydropyrans [71] and 4-dihydropyranones [72] have been prepared by BF_3 or Me_2AlCl catalyzed Diels–Alder reactions of alkyl and aryl aldehydes with dienes **72** and **73** (Equations 3.20 and 3.21). Allylic bis-silanes are useful building blocks for synthesizing molecules of biological interest [73]. 4-Pyranones have been obtained by cerium ammonium nitrate (CAN) oxidation of the cycloadducts.



72 (3.20)

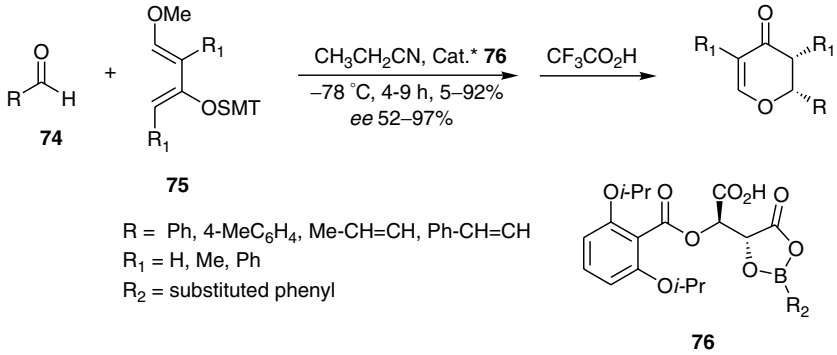
R = Me, Et, *i*-Pr, *i*-Bu, Ph



73 (3.21)

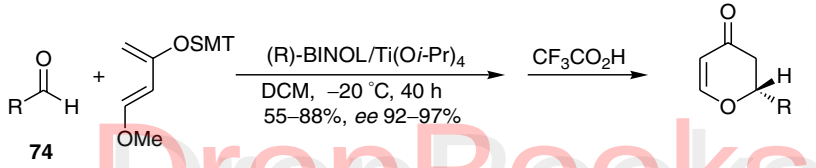
R = Me-CH=CH, Ph, Ph-CH=CH, 2-Fu, C_6H_{11}, CH_2OSPT

The Diels–Alder reaction of aldehydes **74** with dienes **75** in the presence of chiral acyloxyborane (CAB) catalysts **76** provides enantioselectively chiral 4-dihydropyranones (Equation 3.22) after CF_3CO_2H treatment of the cycloadducts [74].



(3.22)

The enantioselection depends greatly on the nature of the R_2 group at the boron atom, and the *ee* values were as high as 97%. High enantioselectivity was observed in the synthesis of 4-dihydropyranones, based on the Diels–Alder reactions of aldehydes **74** and Danishefsky's diene, catalyzed by a BINOL-Ti(O-i-Pr)$_4$-derived catalyst [75] (Equation 3.23).



(3.23)

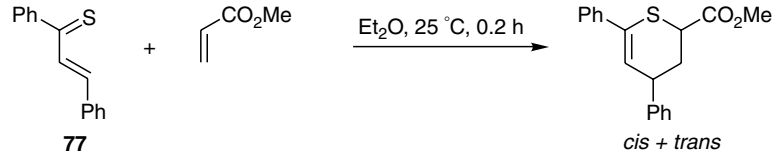
DropBooks

The adduct derived from (α-benzyloxyacetaldehyde (97% *ee*) is an important intermediate en route to compactin and mevinolin [76]. In contrast, modest enantioselectivity was attained when the cycloadditions were catalyzed by a chiral BINOL-ytterbium-derived catalyst [77]. Pyridines were used as additives, and the best enantioselection (93% *ee*) was attained only in the case of *p*-methoxybenzaldehyde using 2,6-lutidine.

Dihydrothiopyrans have also been prepared by cycloaddition between α,β-unsaturated thioketones and carbonyl-activated dienophiles under Lewis-acid catalysis [78]. A marked dependence of the reaction yield on the catalyst was observed. The results of the cycloaddition reaction of thioketone **77** with methyl metacrylate, catalyzed by different catalysts, are illustrated in Equation 3.24.

3.3.2 Inverse Diels–Alder Reactions. Synthesis of Pyranes

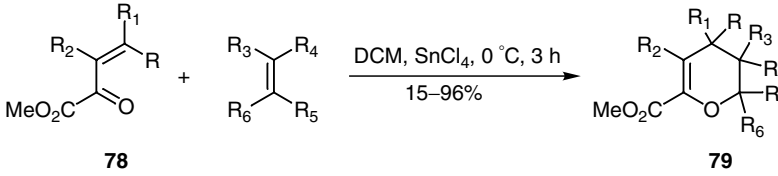
Lewis-acid catalyzed inverse electron-demand Diels–Alder reactions between conjugated carbonyl compounds and simple alkenes and enolethers also allow dihydropyranes to be prepared. $SnCl_4$-Catalyzed cycloaddition of



Cat.	Yield (%)
–	68
$ZnCl_2$	57
i-PrOAlCl_2	75
$AlCl_3$	77
Et$AlCl_2$	93

(3.24)

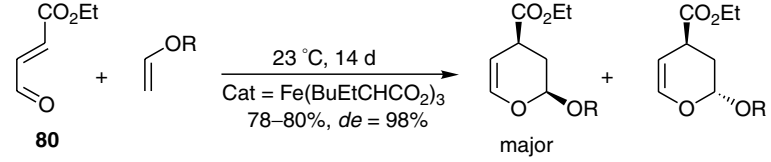
methyl-2-oxo-3-alkenoates **78** with a variety of alkenes [79] afforded dihydropyran derivatives **79** (Equation 3.25).



(3.25)

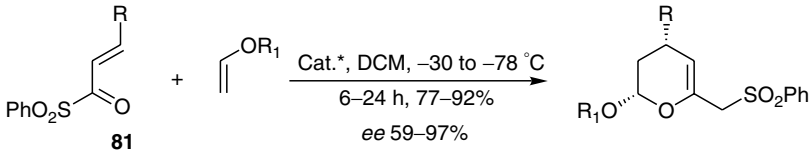
R, R_1, R_2, = H, Me, OMe, Ph; R_3, R_4, R_5, R_6 = H, Me, Et, Bu, $-(CH_2)_4-$

Substituted 3,4-dihydropyranes were also prepared by Diels–Alder reactions between (E)-4-oxobutenoate **80** and vinylethers [80] under iron(III) 2-ethylhexaonate, a mild and economical catalyst (Equation 3.26). Diastereomeric excess as high as 98% was observed. Cycloadducts with a 2,4-*cis*-configuration were preferred.

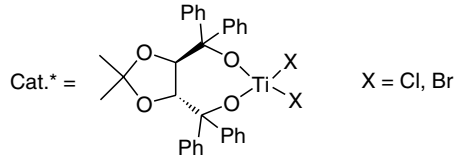


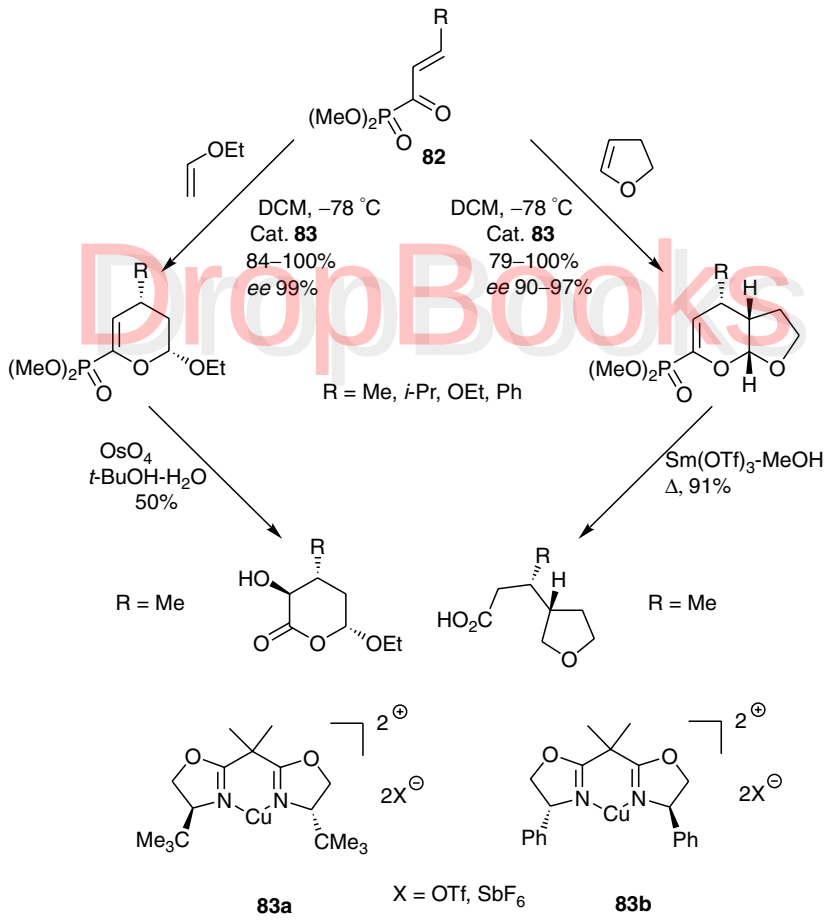
(3.26)

Inverse electron-demand Diels–Alder reaction of (E)-2-oxo-1-phenylsulfonyl-3-alkenes **81** with enolethers, catalyzed by a chiral titanium-based catalyst, afforded substituted dihydro pyranes (Equation 3.27) in excellent yields and with moderate to high levels of enantioselection [81]. The enantioselectivity is dependent on the bulkiness of the R_1 group of the dienophile, and the best result was obtained when R_1 was an isopropyl group. Better reaction yields and enantioselectivity [82, 83] were attained in the synthesis of substituted chiral pyranes by cycloaddition of heterodienes **82** with cyclic and acyclic enolethers, catalyzed by C_2-symmetric chiral Cu(II) complexes **83** (Scheme 3.16).



R = Me, *i*-Pr, Ph; R_1 = Et, *i*-Pr, *i*-Bu (3.27)



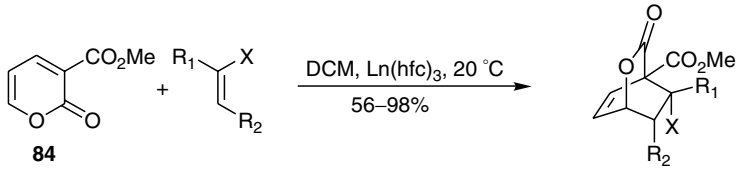


Scheme 3.16

DropBooks

3.3.3 Pyrones and Triazines as Dienes

The 2-pyrones can behave as dienes or dienophiles depending on the nature of their reaction partners. 3-Carbomethoxy-2-pyrone **(84)** underwent inverse Diels–Alder reaction with several vinylethers under lanthanide shift reagent-catalysis [84] (Equation 3.28). The use of strong traditional Lewis acids was precluded because of the sensitivity of the cycloadducts toward decarboxylation. It is noteworthy that whereas $Yb(OTf)_3$ does not catalyze the cycloaddition of **84** with enolethers, the addition of (R)-BINOL generates a new active ytterbium catalyst which promotes the reactions with a moderate to good level of enantioselection [85].

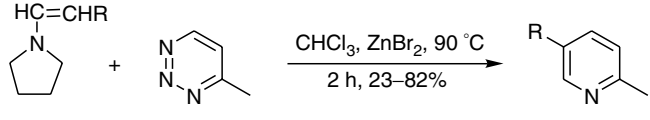


(3.28)

84

X = OR, SR, OSMT Ln = Eu, Pr

2,5-Disubstituted pyridines [86] **87** have been prepared by catalyzed cycloaddition of 4-methyl-1,2,3-triazine **85** with aldehyde enamines **86** (Equation 3.29). The best yields were obtained when $ZnBr_2$ was used as catalyst.



(3.29)

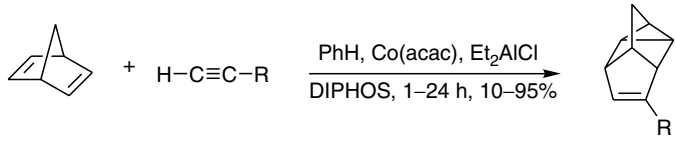
86 **85** **87**

R = Ph, Bn, $Ph(CH_2)_{2-}$, $Me(CH_2)_{n-}$ [n = 2, 3, 5, 10]

3.4 *HOMO*-DIELS–ALDER REACTION

The *homo*-Diels–Alder reaction is a [2 + 2 + 2] cycloaddition of a 1,4-diene with a dienophile which produces two new bonds and a cyclopropane ring. This reaction is an example of a multi-ring-forming reaction that to date has found few applications in synthesis, since the use of 1,4-dienes has been limited mainly to bridged cyclohexa-1,4-dienes and almost exclusively to norbornadiene. Lewis-acid catalysts accelerate *homo*-Diels–Alder reactions and increase the selectivity for the [2 + 2 + 2] vs. [2 + 2] cycloaddition.

A cobalt-based catalyst, prepared by reducing $Co(acac)_3$ with diethylaluminum chloride in the presence of the bidentate ligand 1,2-bis(triphenylphosphino)ethane, accelerates [87] the cycloadditions of norbornadiene **(88)** with a variety of acetylenes (Equation 3.30).

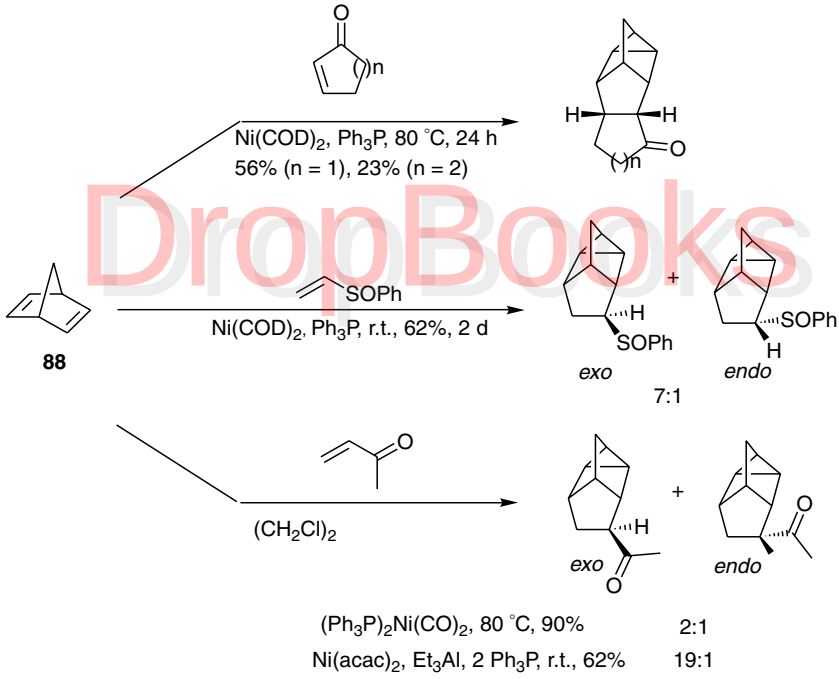


(3.30)

88 **89**

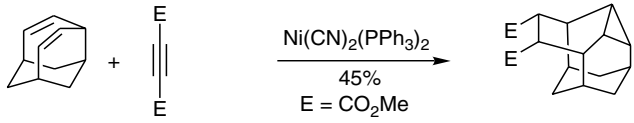
R = H, Me, Et, *i*-Pr, Bu, *t*-Bu, Ph, $CH_2CH(OAc)CH_2CH_3$, $(CH_2)_4$-OPMB, $(CH_2)_3$-OSMDBT

This route provides a convenient method for synthesizing deltacyclenes **89** which have been proven to be useful in the synthesis of highly strained unnatural products of theoretical interest [88]. Diels–Alder reactions of norbornadiene **(88)** have been successfully activated by a nickel catalyst [89] (Scheme 3.17). A marked influence of the catalyst on the *endo–exo* diastereoselectivity has been observed.



Scheme 3.17

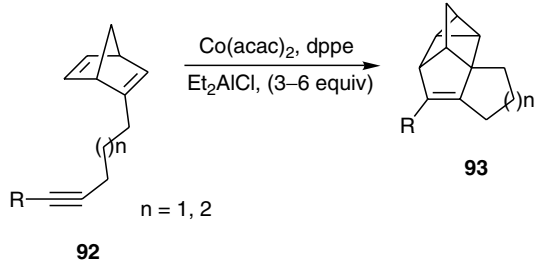
An example that illustrates the influence of the nickel catalyst on the reaction yield is the cycloaddition between tricyclo [5.3.1.$0^{4,9}$]-undeca-2,5-diene **(90)** and dimethylacetylenedicarboxylate (Equation 3.31). Whereas a thermal process afforded cycloadduct **91** in an unsatisfactory yield (22 %), the catalyzed process



90 91 (3.31)

increased the yield up to 45%. This reaction has been used to construct the didehydrohomoiceane skeleton [90].

Lewis-acid catalysis is effective in intermolecular as well as intramolecular *homo*-Diels–Alder reactions. Thus, complex polycyclic compounds **93** have been obtained in good yield by the cycloaddition of norbornadiene-derived dienynes **92** by using cobalt catalyst, whereas no reaction occurred under thermal conditions [91] (Scheme 3.18).



92 93

n	1	1	1	1	2	2	2
R	H	Me	TMS	Ph	H	Me	TMS
Yield (%)	78	69	63	70	64	43	48

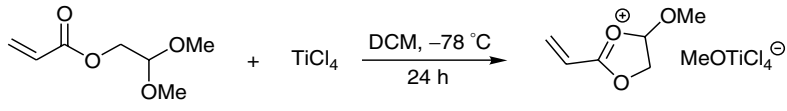
Scheme 3.18

3.5 CATIONIC DIELS–ALDER REACTION

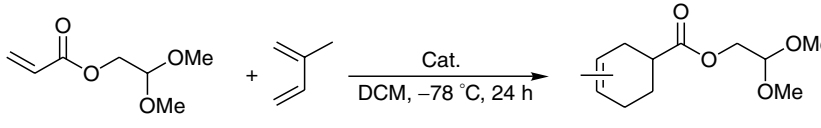
The cationic moiety attached to the carbon–carbon double bond is a strong electron-withdrawing group that increases the dienophilic character of the double bond in the Diels–Alder reaction.

2,2-Dimethoxyethylacrylate **(94)** may be readily converted into the cationic species **95** by the action of Lewis acids [92] (Equation 3.32); the cationic species then undergoes Diels–Alder reaction with a variety of dienes. The type of catalyst markedly affects the reaction yield, stereoselectivity and regioselectivity as shown in Scheme 3.19 and Equation 3.33.

Another model cationic species [92] that has been studied is cation **99** which is obtained from 2-oxopropylacrylate **98**. By treating compound **98** with equimolecular amounts of trimethylsilyltrifluoromethane sulfonate and methoxytrimethylsilane in the presence of 1,3-cyclohexadiene, a cycloadduct is produced



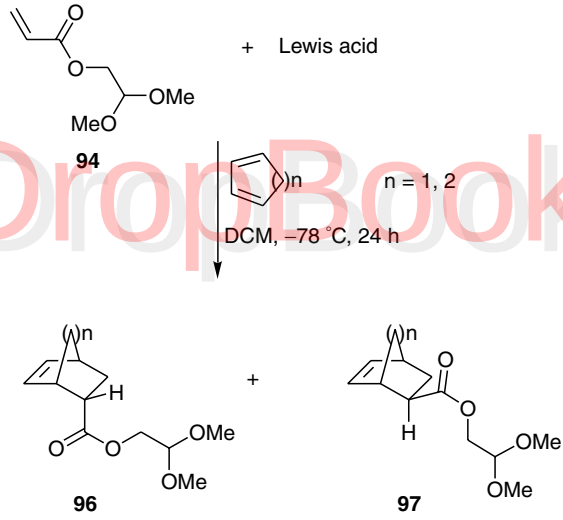
(3.32)



(3.33)

Cat.	Yield (%)	*para:meta*
$TiCl_4$	66	97:3
Me_3SiOTf	78	>99:< 1

in 89 % yield (Equation 3.34). It should be noted that the addition of methoxytrimethylsilane is essential for the generation of the allylcation intermediate.



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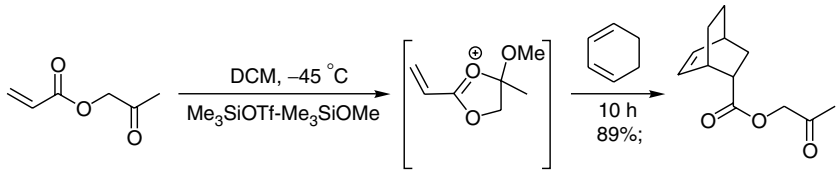
n	Lewis-acid	Yield (%)	**96:97**
1	$TiCl_4$	85	25:1
1	Me_3SiOTf	41	34:1
1	$BF_3\ OEt_2$	21	69:1
1	$GaCl_3$	84	45:1
2	$TiCl_4$	89	100:0
2	Me_3SiOTf	83	100:0

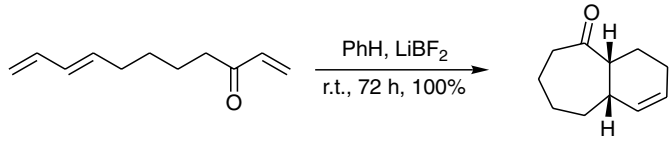
Scheme 3.19



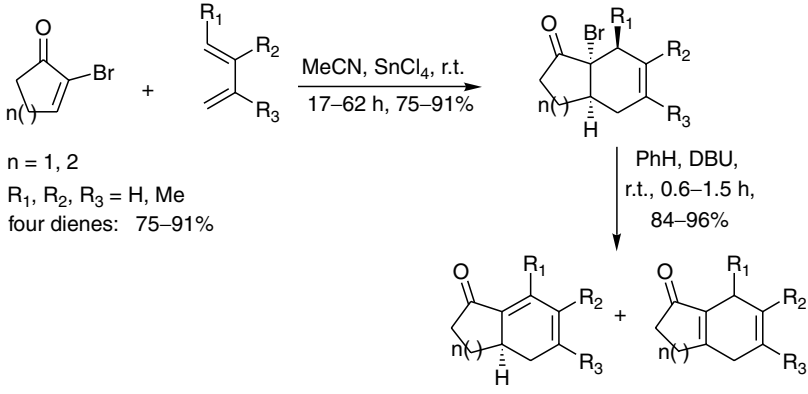
(3.34)

3.6 OUTLINED DIELS–ALDER RECTIONS

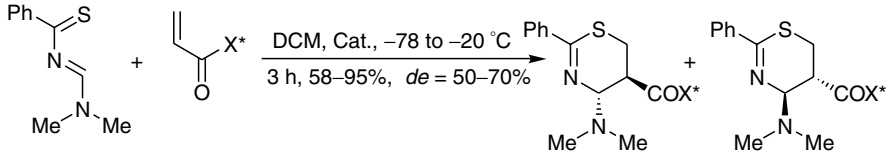
$LiBF_4$: a mild Lewis-acid for intramolecular Diels–Alder reactions [93]

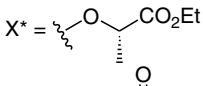


Diels–Alder reactions of 2-bromo-2-cycloalkenones. A convenient approach to doubly cisoid fully conjugated dienone system [94]

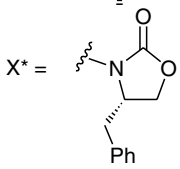


An asymmetric route to the 5,6-dehydro-4H-1,3-thiazine skeleton via an asymmetric *hetero*-Diels–Alder reaction [95]



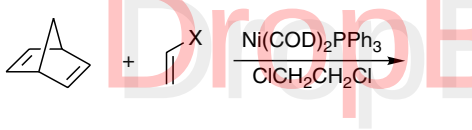


Cat = $TiCl_4$, $TiCl_2(O\text{-}iPr)_2$, $EtAlCl_2$, Et_2AlCl, $MgBr_2$; Yield: 58–90%

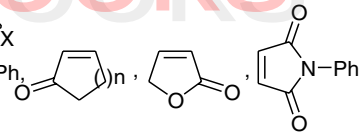


Cat = $MgBr_2$; Yield: 95%, *de* = 100%

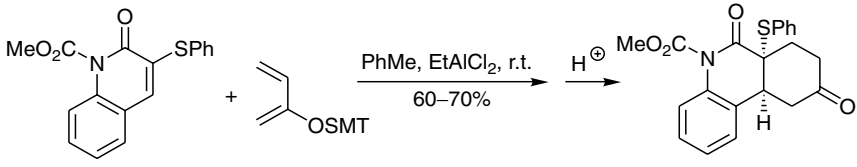
Nickel-catalyzed $[2\pi + 2\pi + 2\pi]$ (*homo*-Diels–Alder) and $[2\pi + 2\pi]$ cycloadditions of bicyclo[2.2.1]hepta-2,5-dienes [96]



Dienophiles: X = CHO, COMe, CO*t*-Bu, CN, SOPh, SO_2Ph,



Lewis-acid-catalyzed Diels–Alder reaction of 3-phenylthio-2- quinolinones with siloxydiene. Synthesis of the intermediate for dynemicin A core [97]



no reaction without catalyst.

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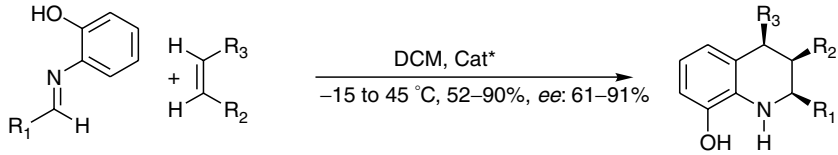
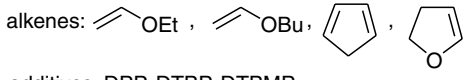
Catalytic asymmetric aza-Diels–Alder reactions using a chiral lanthanide Lewis acid. Enantioselective synthesis of tetrahydroquinoline derivatives using a catalytic amount of a chiral source [98]

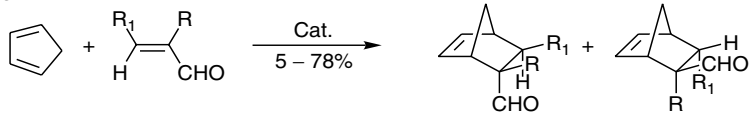


R_1, = Ph, α-Napht, C_6H_{11}

alkenes: 

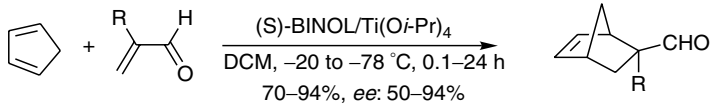
additives: DPP, DTBP, DTBMP

Investigations into the use of niobium and tantalum complexes as Lewis acids [99]



R, R_1= H, Me

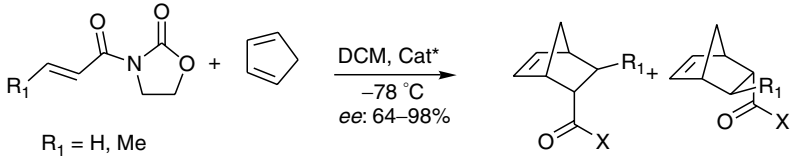
A simple and practical synthesis of (+)-2- bromobicyclo [2.2.1]hept-5-ene-2-carboxaldehyde via chiral Lewis-acid catalyzed [4 + 2] cycloaddition [100]



R = Me, Br

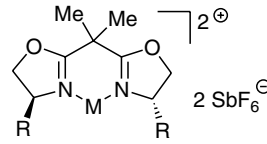
endo/ exo = 17:1

Cationic bis(oxazoline) and pyridil-bis(oxazoline) Cu(II) and Zn(II) Lewis-acid catalysts. A comparative study in catalysis of Diels–Alder and aldol reactions [101]



R_1 = H, Me

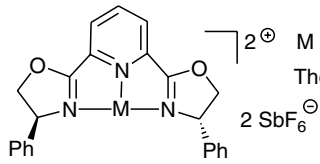
Cat*



R = *t*-Bu, M = Cu

R = Ph, M = Zn

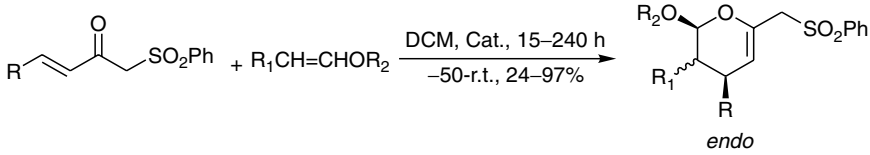
Cat*



M = Cu, Zn

The Cu-based catalysts were found to be superior

Exclusively endo-selectivity Lewis-acid catalyzed *hetero*-Diels–Alder reactions of (E)-1-phenylsulfonyl-3-alken-2-ones with vinylethers [102]

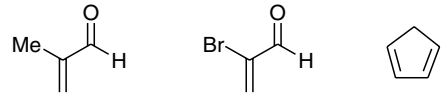


R = H, Me, *i*-Pr, Ph; R_1 = H, Me, Ph; R_2 = Et, *i*-Bu, Ph

Cat = ZnI_2, $Eu(fod)_3$, $TiCl_2(O\textit{i}\text{-}Pr)_2$

Chiral Lewis acids supported on silica gel and alumina, and their use as catalysts in Diels–Alder reactions of methacrolein and bromoacrolein [103]

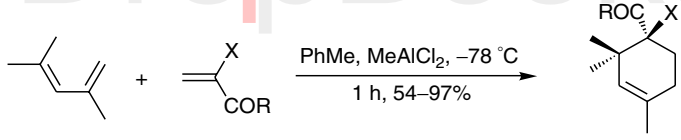
Derivatives of (S)-tyrosine were supported on silica gel through the phenolic oxygen atom and treated with BH_3 to give Lewis acids able to accelerate the Diels–Alder reactions of methacrolein and bromoacrolein with cyclopentadiene. (S)-Prolinol has been supported on silica gel and alumina and then treated with $EtAlCl_2$ to give a supported catalyst.



The observed enantioselectivity was zero or very low.

DropBooks

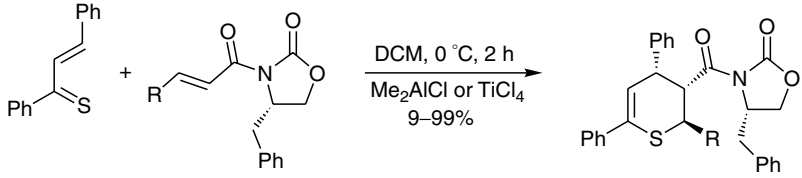
Highly selective Lewis-acid-catalyzed Diels–Alder reactions of acyclic (Z)-1,3-dienes [104]



X = H, Me, OAc; R = H, NHBz

four dienes; six dienophiles; catalyst: $MeAlCl_2$, $SnCl_4$

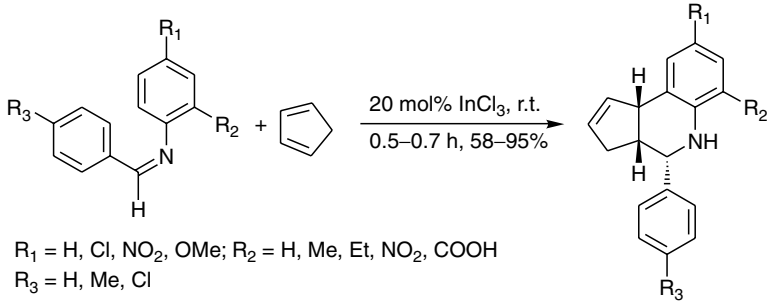
Lewis-acid-catalyzed asymmetric hetero-Diels–Alder cycloaddition of a 1-thiabuta-1,3-diene with chiral *N*-acryloyl and *N*-crotonyl oxazolidinone dienophile [105]



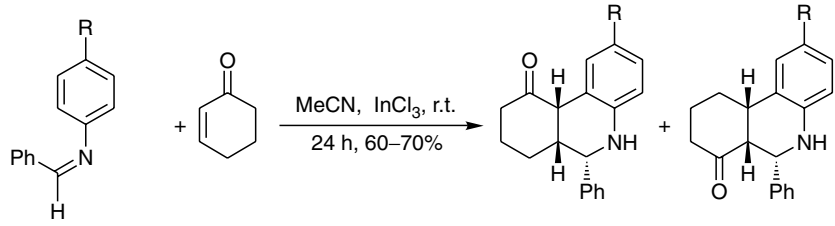
R = H, Me

endo:exo = 99:1 to 61:39

Imino Diels–Alder reactions catalyzed by indium trichloride ($InCl_3$). Facile synthesis of quinoline and phenanthridinone derivatives [106]

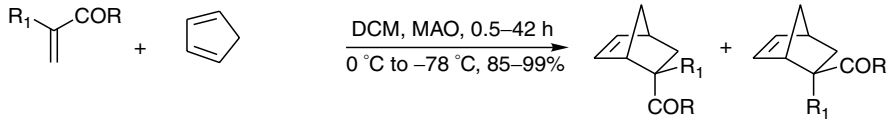


R_1 = H, Cl, NO_2, OMe; R_2 = H, Me, Et, NO_2, COOH
R_3 = H, Me, Cl

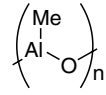


R = H, Cl, NO_2, OMe

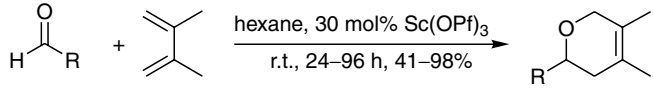
Methylalumoxane as a highly Lewis-acidic reagent for organic synthesis [107]



R = H, Me, OMe; R_1 = H, Me

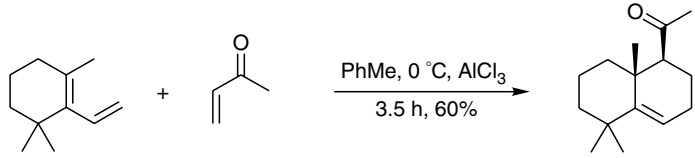
Methylalumoxane = MAO = 

Scandium(III) perfluorooctanesulfonate [$Sc(OPf)_3$]: a novel catalyst for the hetero-Diels–Alder reaction of aldehydes with non-activated dienes [108]



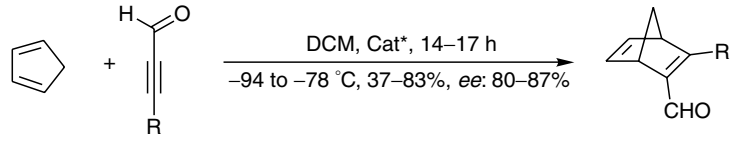
R = Ph, *p*-XC_6H_4 (X = NO_2, Cl, Me, OMe, Ph, NO_2),
-Naphthyl, $PhCH_2CH_2$, C_6H_{11}, C_6H_{13}

Synthesis of decalin synthons of bioactive terpenoids: Lewis-acid-catalyzed Diels–Alder reactions [109]

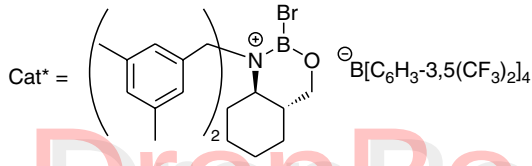


six dienophiles: 35–80%

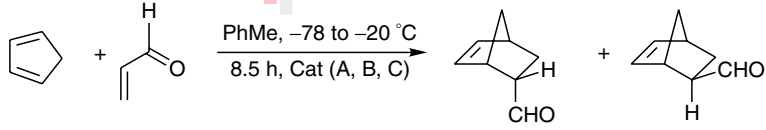
Enantioselective Diels–Alder reactions between cyclopentadiene and α,β-acetylenic aldehydes catalyzed by a chiral super Lewis acid [110]



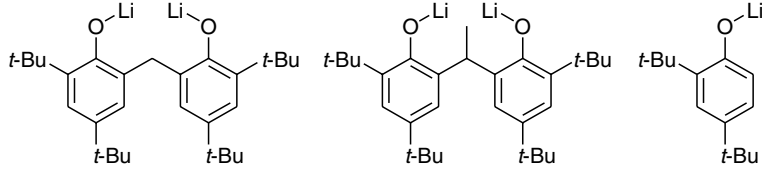
R = TMS, TES, Me_2PhSi, Bu_3Sn



Dilithium 2,2′-methylenebis(4,6-di-*tert*-butylphenoxide) as a bidentate Lewis acid in organic synthesis [111]

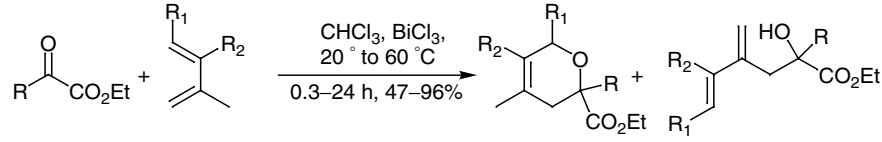


Cat.	*Endo/Exo*		Yield (%)
A	76	24	77
B	81	19	50
C	–	–	traces



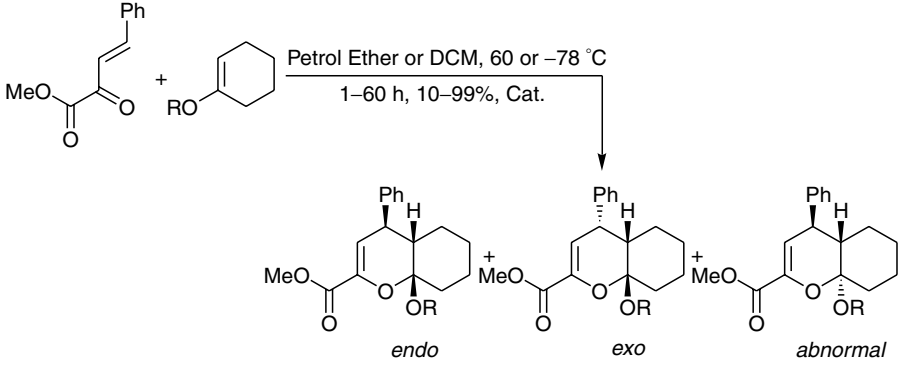
DropBooks

The carbonyl Diels–Alder reaction catalyzed by bismuth(III) chloride [112]



R = H, CO_2Et; R_1, R_2 = H, Me

$Eu(fod)_3$ and $SnCl_4$-catalyzed heterocycloadditions of *o*-silylenol ethers deriving from cyclic ketones [113]



R = Me, $SiMe_2t$-Bu, $SiPh_2t$-Bu, $SiMe_3$; Cat = $Eu(fod)_3$, $SnCl_4$, $TiCl_4$

In the presence of $Eu(fod)_3$ the *endo*-cycloadduct is the predominant reaction product; in the presence of $SnCl_4$ the *abnormal* product is predominant

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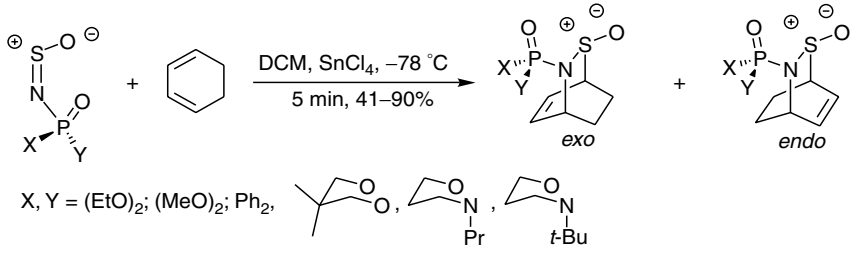
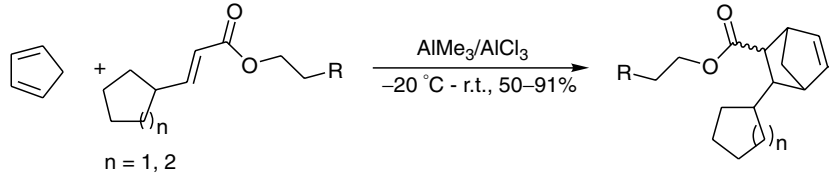
Reactivity and diastereoselectivity in the thermal and Lewis-acid-catalyzed Diels–Alder reactions of *N*-sulphinylphosphoramidates [114]

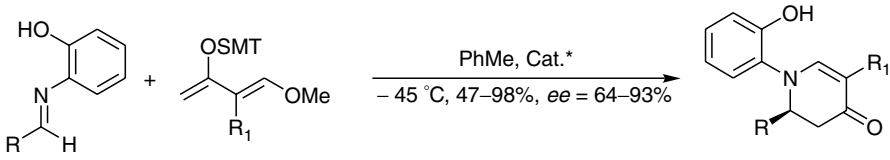


Lewis-acid-catalyzed Diels–Alder reactions of highly hindered dienophiles [115]

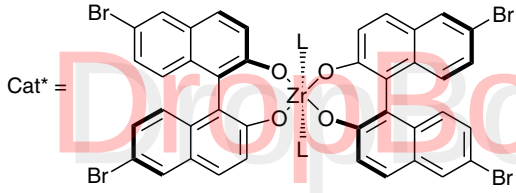


R = Me, Ph; *endo/exo* from 2:1 to 7:1

The first enantioselective aza-Diels–Alder reactions of imino dienophiles on use of a chiral zirconium catalyst [116]

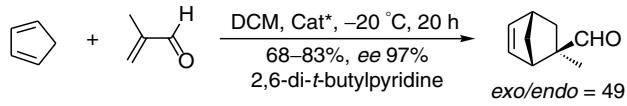


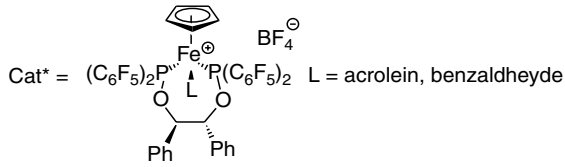
R = α-Naphthyl, *o*-MeC$_6$H$_4$, Ph, Me(OMe)$_2$C$_6$H$_3$, 2-Thienyl, Cy;
R$_1$ = H, Me; L = NMI, DMI



DropBooks

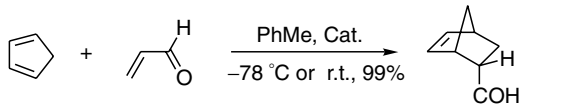
A new chiral ligand for the Fe-Lewis-acid catalyzed asymmetric Diels–Alder reaction [117]





three aldehydes: three dienes

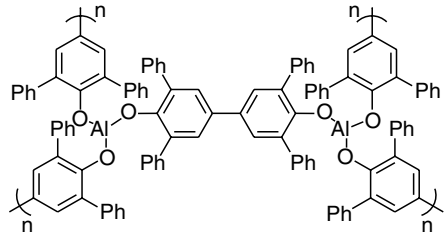
Aluminum trisphenoxide polymer as a Lewis-acidic solid catalyst [118]



endo/exo = 3.5

four dienophiles, three dienes:

Cat =


n
Ph
Ph
Ph
O
Al
O
Ph
Ph
n
Ph
Ph
Ph

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4 Diels–Alder Reaction Facilitated by Special Physical and Chemical Methods

The Diels–Alder reaction is the most widely used carbon–carbon, carbon–heteroatom and heteroatom–heteroatom bond-forming reaction for the construction of six-membered rings; therefore it is not surprising that many methods have been used to accelerate the reaction and to improve its selectivity. Chapters 2, 3 and 5 illustrate the effects of temperature, Lewis acids and pressure, respectively; this chapter provides a survey of other physical and chemical methods by which the Diels–Alder reaction can be profitably carried out.

A compendium of these special methods was reviewed by Pindur in 1993 [1].

4.1 SOLID-PHASE DIELS–ALDER REACTION

DropBooks

Solid-phase chemistry is an efficient synthetic tool that, compared with solution-phase chemistry, simplifies the work-up of the reaction, allows the process to be driven to completion by using excess of reagents, and can be automatized [2a]. In recent years, many studies have been devoted to developing both surface-mediated and resin-supported synthesis. Today the solid-phase approach is not limited to peptides and oligonucleotides but is also used to synthesize molecules of lower molecular weight.

The Diels–Alder reaction on solid support was first performed 20 years ago and is now a consolidated procedure [2b].

4.1.1 Inorganic Solid-Surface-Promoted Diels–Alder Reaction

Porous surfaces of inorganic solids such as clays, silica gel, alumina and zeolites are the commonest systems used as catalysts in Diels–Alder reactions.

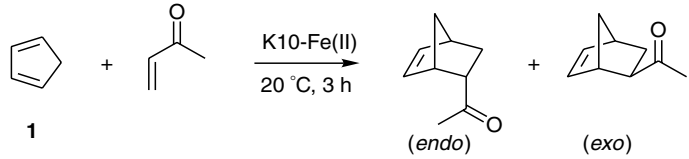
Two classes of clays are known [3]: (i) cationic clays (or clay minerals) that have negatively charged alumino-silicate layers balanced by small cations in the interlayer space (e.g. K-10 montmorillonite) and (ii) anionic clays which have positively charged brucite-type metal hydroxide layers balanced by anions and water molecules located interstitially (e.g. hydrotalcite, $Mg_6Al_2(OH)_{16}CO_3 4H_2O$.

It is believed that clay minerals promote organic reactions via an acid catalysis [2a]. They are often activated by doping with transition metals to enrich the number of Lewis-acid sites by cationic exchange [4]. Alternative radical pathways have also been proposed [5] in agreement with the observation that clay-catalyzed Diels–Alder reactions are accelerated in the presence of radical sources [6].

Montmorillonite K-10 doped with Fe(III) efficiently catalyzes the Diels–Alder reaction of cyclopentadiene **(1)** with methyl vinyl ketone at room temperature [7] (Table 4.1). In water the diastereoselectivity is higher than in organic media; in the absence of clay the cycloaddition proceeds at a much slower rate.

By using unactivated K-10 montmorillonite in the absence of solvent, the *endo–exo* selectivity of the cycloadditions of acrolein and methyl vinyl ketone with cyclopentadiene and cyclohexadiene is low [8] (Table 4.2, entry 3), while highly reactive dienophiles such as 1,4-benzoquinone and N-phenyl

Table 4.1 Diels–Alder reactions of cyclopentadiene (**1**) with methyl vinyl ketone catalyzed by Fe(II)-K-10 montmorillonite in various solvents



Medium	*endo/exo*	Yield (%)
H_2O	19:1	95
CH_2Cl_2	9:1	97
EtOH	14:1	95

Table 4.2 Solvent-free Diels–Alder reactions in the presence of unactivated K-10 montmorillonite at 0 °C

Entry	Diene[a]	Dienophile[b]	*t*(h)	*endo/exo*	Yield (%)
1	CP	BQ	5	>99	70
2	CP	NPM	14	>99	98
3	CP	MVK	3	10	95
4	CP	AC	3[c]	5	78
5	CH	BQ	8	>99	64
6	CH	NPM	6	>99	86
7	CH	MVK	2[d]	19	78
8	CH	AC	2[d]	11	50

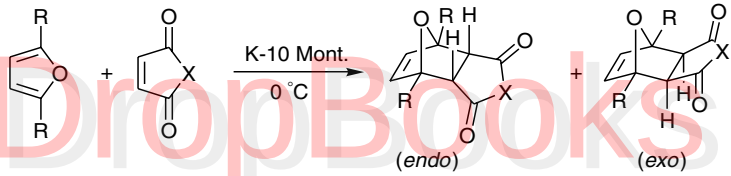
[a] CP = cyclopentadiene, CH = 1,3-cyclohexadiene;
[b] BQ = 1,4-benzoquinone, NPM = N-phenyl maleimide, MVK = methyl vinyl ketone, AC acrolein;
[c] at −25 °C;[
[d] at 25 °C

maleimide give exclusively *endo* addition (Table 4.2). A parallel study carried out in the presence of alumina revealed that reactions on the surface of K-10 montmorillonite are faster and give higher yields and that the beneficial effect of alumina is dependent on its degree of activation.

The investigation on the use of K-10 montmorillonite under free solvent conditions was then extended to inner ring dienes such as furan and its 2,5-dimethyl derivative [9] (Table 4.3). The cycloadditions generally proceed slowly, and Zn(II)-doped clay and microwave irradiation were used to accelerate the reactions. The reaction with maleic anhydride preferentially affords the thermodynamically favored *exo* adduct.

Clay-catalyzed asymmetric Diels–Alder reactions were investigated by using chiral acrylates [10]. Zn(II)- and Ti(IV)-K-10 montmorillonite, calcined at 55 °C, did not efficiently catalyze the cycloadditions of cyclopentadiene **(1)** with acrylates that incorporate large-size chiral auxiliaries such as *cis*-3-neopentoxyisobornyl acrylate **(2)** and (–)-menthyl acrylate (**3**, R = H) (Figure 4.1). This result was probably due to diffusion problems.

Table 4.3 Solvent-free Diels–Alder reactions in the presence of unactivated K-10 montmorillonite



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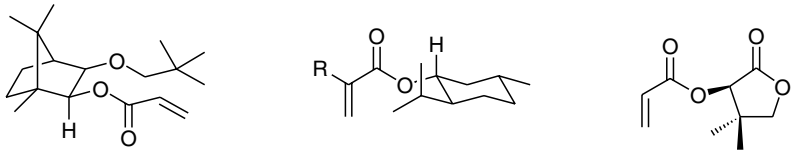
R	X	*t* (h)	*T* (°C) or MW[a]	*endo/exo*	Yield (%)
H	NPh	24	0	1.3:1	85
H	NPh	0.25	MW[b]	1.5:1	80
H	O	3	0	1:3	36
H	O	0.03	MW[c]	1:3	16
Me	NPh	1.5	0	2.3:1	77
Me	NPh	0.17	MW[b]	2.3:1	100

[a] Microwave irradiation;
[b] 150 W;
[c] 300 W



2 **3** **4**

Figure 4.1

Table 4.4 Diels–Alder reactions of (R)-O-acryloylpantolactone (***4***) with cyclopentadiene (**1**) in methylene chloride

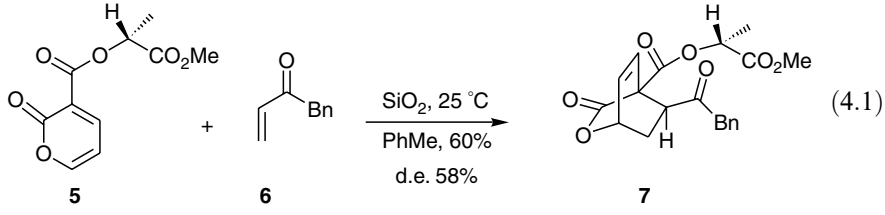
Catalyst	T (°C)	1/4[a]	t(h)	*endo/exo*	d.e. (%)	Yield (%)
none	20	6:1	24	75:25	6	100
$TiCl_4$	−10	1.5:1	0.5	99:1	92	100
$EtAlCl_2$	−10	1.5:1	1	99:1	42	94
Zn-120	20	5:1	24	93:7	43	97
Fe-550	20	5:1	24	98:2	39	98
Ti-550	20	3:1	2	90:10	43	94

[a] Molar ratio

Good results were obtained with (R)-O-acryloylpantolactone **(4)** in which the dienophile was incorporated with a smaller chiral auxiliary. Some results are reported in Table 4.4, where the cycloadditions catalyzed by Zn(II)-, Fe(II)- and Ti(IV)-K-10 exchanged montmorillonite calcined at 120 °C and 550 °C are compared with those that were not catalyzed and with $TiCl_4$- and $EtAlCl_2$-catalyzed reactions. Among the metal-clays activated, the Ti(IV)-K-10 was the best catalyst with high conversion and acceptable enantioselectivity obtained after 2 h.

Silica gel [11] or alumina [11a, 12] alone, or silica and alumina together modified by Lewis-acid treatment [13] and zeolites [14], have been widely used as catalysts in Diels–Alder reactions, and these solids have also been tested as catalysts in asymmetric Diels–Alder reactions [12,13b,14]. Activated silica gel and alumina at 140 °C were used [15] to catalyze the asymmetric cycloaddition of (–)-menthyl-N-acetyl-α,β-dehydroalaninate **(3)** (R = NHCOMe) with cyclopentadiene in the key step for synthesizing optically active cycloaliphatic α-amino acids. When the reactions were carried out in the absence of solvent, a higher conversion was obtained. Some results are reported in Table 4.5 and compared with those obtained by using silica and alumina modified by treatment with Lewis acids. Silica gel gives a reasonable percentage of conversion after 24 h with complete diastereofacial selectivity in *exo* addition.

Commercial chromatography silica gel promotes effectual Diels–Alder cycloaddition of optically active pyrone lactate ester (**5**) with benzyl vinyl ether **(6)**, affording the *endo* adduct **7** in an approximately 4:1 mixture of diastereoisomers [16] (Equation 4.1).



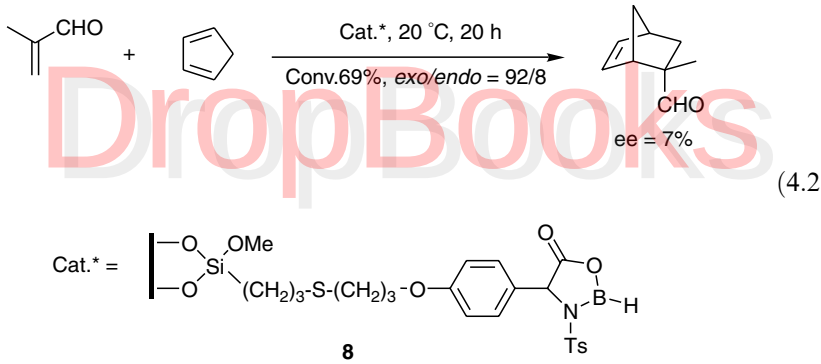
5 **6** **7** (4.1)

Table 4.5 Solvent-free Diels–Alder reactions of (−)-menthyl N-acetyl-α,β-dehydroalaninate (**3**, R = NHCOMe) with cyclopentadiene (**1**) at 25 °C

Catalyst	*C* (%)[a]	*endo/exo*	d.e. (*endo*)	d.e. (*exo*)
SiO_2-140	88	29:71	70:30	>97:3
Al_2O_3-140	55	36:64	69:31	>97:3
$SiO_2 + Et_2AlCl$	49	33:67	80:20	>97:3
$SiO_2 + TiCl_4$	45	39:61	75:25	>97:3

[a] Conversion after 24 h
[b] Related to ester group

Oxazoborolidinone **8** is an example of catalyst supported on silica gel. It is prepared by immobilizing the N-tosyl-O-allyl-(S)-tyrosine with mercaptopropyl silica and treatment with BF_3 and has been used to catalyze the Diels–Alder reaction of methacrolein with cyclopentadiene [17] (Equation 4.2). The cycloaddition occurs with good diastereoselectivity but with low enantioselectivity.



(4.2)

8

Better enantiomeric excess was obtained by using (–)-menthol-aluminum Lewis acids supported on silica gel and alumina through the aluminum atom [17].

Pagni and coworkers [18] have conducted in-depth investigations on the cycloadditions of cyclopentadiene with methyl acrylate on alumina of varing activity (200 °, 300 °, 400 °, 800 °) showing that the diastereoselectivity of the reaction is markedly dependent on the activity of the alumina. The *exo/endo* ratio goes up significantly on 400 °-Al_2O_3 having a value of 52 for 10:1 w/w ratio of Al_2O_3 to reactants. Unexpectedly the *exo/endo* ratio dropped to 0.93 when the reaction was run on 800 °-Al_2O_3. These results were explained on the basis of stability and epimerization of adducts.

Catalysis of Diels–Alder reaction by zeolites is predominantly physical rather than chemical in nature [19]. The reactants are concentrated internally in cavities

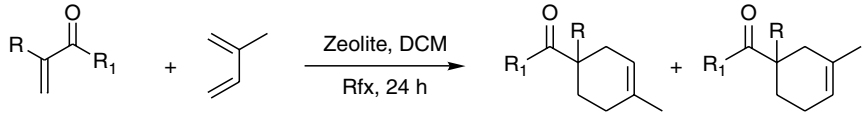
of material, which provides two advantages: (i) by increasing the reactant concentration inside the zeolite pores, the rate of bimolecular reaction such as the Diels–Alder cycloaddition is enhanced; in this regard, the effect of zeolites is comparable to that obtained with the use of high pressure; and (ii) the geometry of the zeolite cavities influences the regio- and stereoselectivity of the reaction. The nature of the zeolites therefore has a great influence on the reactivity and selectivity of the process.

The use of zeolites is particularly advantageous for self-Diels–Alder reactions of gaseous dienes because it reduces the polymerization of the reactant. An example is the cyclodimerization of 1,3-butadiene to 4-vinylcyclohexene [20a] carried out at 250 °C with satisfactory conversion when non-acidic zeolites, such as large-pore zeolites Na-ZSM-20, Na-β and Na-Y, are used.

The ability of zeolites to control the regioselectivity of Diels–Alder reaction has been investigated for the cycloaddition of isoprene with various dienophiles [20b]. Some results are reported in Table 4.6. All the zeolites tested afforded high regioselectivity but the reaction yield was generally low and depended on the zeolite as well as on the dienophile.

Good yields and high diastereoselectivities were obtained by using zeolites in combination with Lewis-acid catalyst [21]. Table 4.7 illustrates some examples of Diels–Alder reactions of cyclopentadiene, cyclohexadiene and furan with methyl acrylate. Na-Y and Ce-Y zeolites gave excellent results for the cycloadditions of carbocyclic dienes, and combining these zeolites with anhydrous $ZnBr_2$ further enhanced the *endo* diastereoselectivity of the reaction. An exception is the cycloaddition of furan that occurred considerably faster and with better yield, in comparison with the classic procedure [22], when performed in the presence of sole zeolites.

Table 4.6 Diels–Alder reactions catalyzed by zeolites

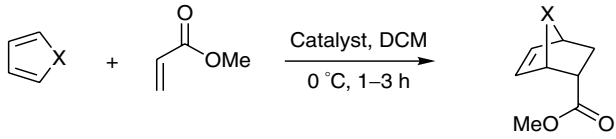


9 **10**

R	R_1	Y-152		Y-45		ZSM-5		Mordenite		Beta	
		9/10	Yield[a]	**9/10**	Yield[a]	**9/10**	Yield[a]	**9/10**	Yield[a]	**9/10**	Yield[a]
Me	H	95:5	55	94:6	69	98:2	100	97:3	91	97:3	62
Me	Br	94:6	40	93:7	53	87:13	23	85:15	34	94:6	39
OMe	H	97:3	48	97:3	31	100:0	11	96:4	33	99:1	100

[a] yield(%)

Table 4.7 Diels–Alder reactions of carbo-and heterocyclic dienes with methyl acrylate catalyzed by zeolites and $ZnBr_2$-doped zeolites



Catalyst	X	*endo* (%)	Yield (%)
Na-Y	CH_2	90	96
$NaY/ZnBr_2$	CH_2	96	98
Ce-Y	CH_2	90	96
$CeY/ZnBr_2$	CH_2	96	100
$NaY/ZnBr_2$	$(CH_2)_2$	85	95
$CeY/ZnBr_2$	$(CH_2)_2$	90	100
Ce-Y	O	40–50[a]	70
$CeY/ZnBr_2$	O	40[a]	70

[a] Reaction time 24 h

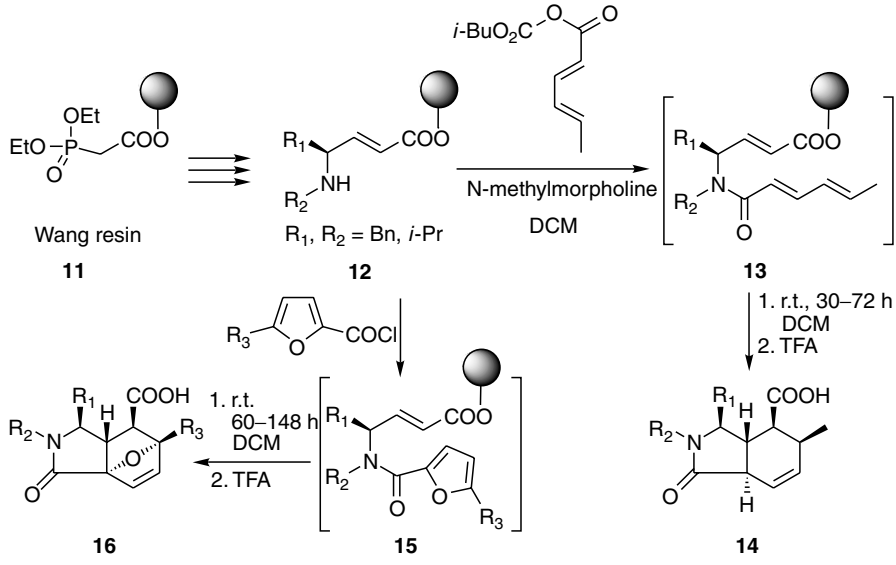
4.1.2 Diels–Alder Reaction Using Resin-Anchored Reagents

DropBooks

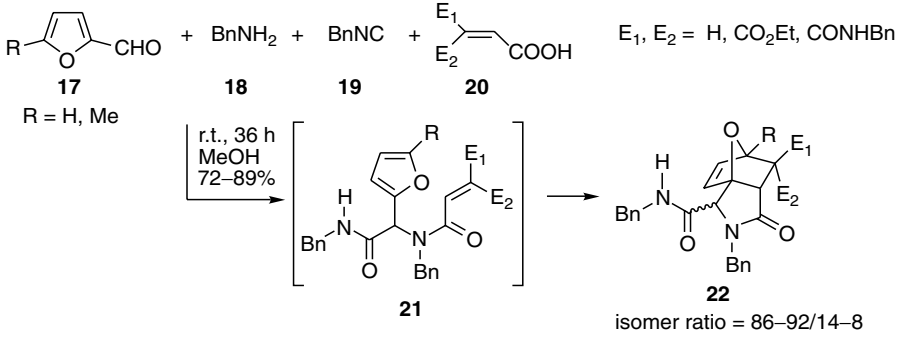
A solid-phase Diels–Alder reaction that uses polymer-supported reagents has recently attracted considerable attention and its use is expanding rapidly.

Intramolecular Diels–Alder reactions of amino acid-derivative trienes **13** (Scheme 4.1) onto solid support have been used for rapid stereoselective synthesis of heterocyclic compounds for high throughput drug screening [23]. The synthesis starts from phosphono-acetyl-Wang resin **11** which is converted to secondary amines **12** and then to resin-bound trienes **13** by acylation reaction. Trienes **13** cyclize at room temperature giving predominant *trans*-fused bicyclic adducts **14**. Trienes **15**, containing a furyl as diene, were prepared similarly and their cycloadditions also proceeded at room temperature to give 1,4-epoxyisohydroindolines **16** which were derived from an *endo* transition state pathway. The resin was cleavaged with TFA-DCM.

The synthesis of highly substituted rigid tricyclic nitrogen heterocycles via a tandem four-component condensation (the Ugi reaction)/intramolecular Diels–Alder reaction was investigated in both solution and solid phase [24]. The Ugi reaction in MeOH (Scheme 4.2) involves the condensation of furylaldehydes **17**, benzylamine **18**, benzyl isocyanide **19** and maleic or fumaric acid derivatives **20**, and provides the triene **21** which immediately undergoes an intramolecular Diels–Alder reaction, affording the cycloadduct **22** in a diastereoisomeric mixture with high yield.

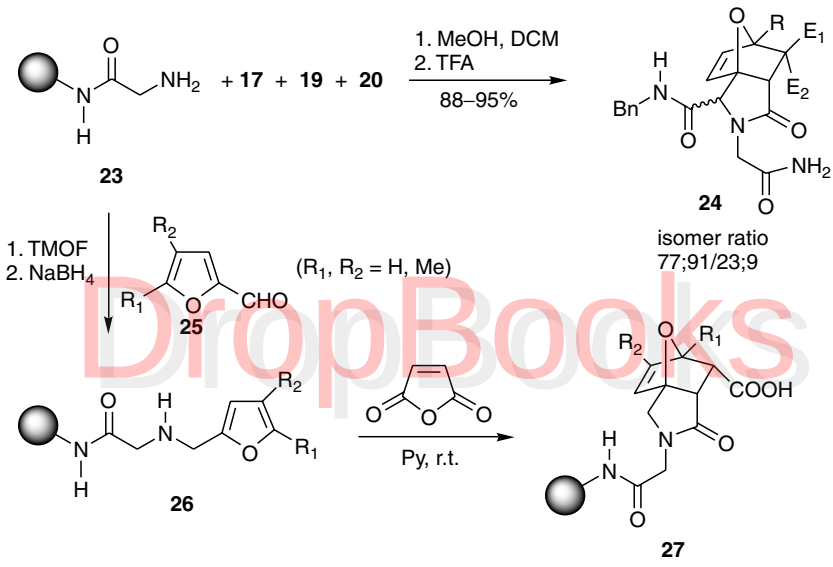


Scheme 4.1



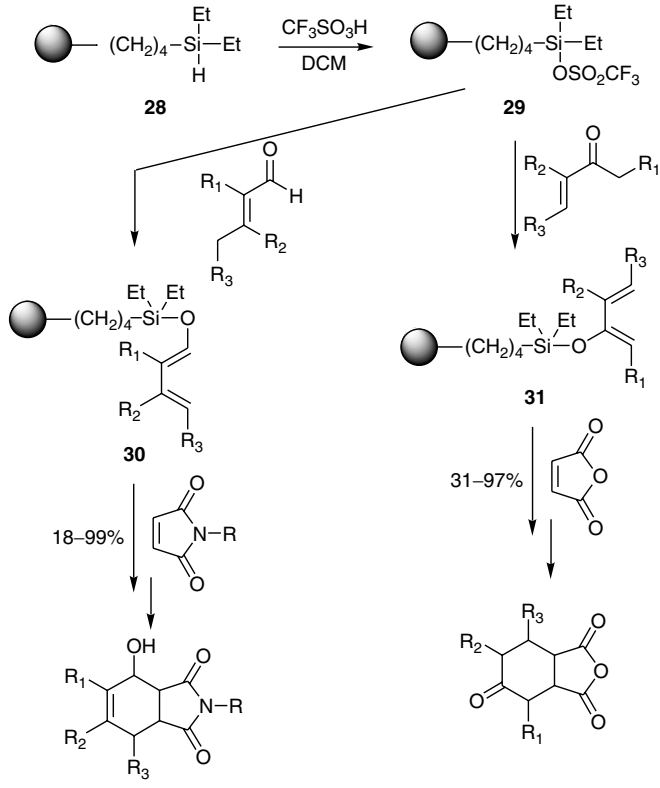
Scheme 4.2

The solid-phase synthesis carried out on acid labile Argo Gel-Rink resin, by using the resin-bound amine **23**, gives cycloadducts **24** with similar results [24] (Scheme 4.3). Another efficient approach to these tricyclic nitrogen heterocycles consists of treating the immobilized amine **23** with excess of furylaldehydes **25** in trimethyl orthoformate [25] (TMOF). Reduction of the resulting imine with $NaBH_4$ furnishes the furylamines **26** which, in the presence of maleic anhydride, gives the cycloadduct **27** via an initial N-acylation followed by an intramolecular Diels–Alder reaction. The resin-bound carboxylic acid **27** was used as a key intermediate for preparing a number of derivatives.



Scheme 4.3

A novel and versatile method for preparing polymer-supported reactive dienes was recently developed by Smith [26]. PS-DES (polystyrene diethylsilane) resin **28** treated with trifluoromethanesulfonic acid was converted to a polymer-supported silyl triflate **29** and then functionalized with enolizable α,β-unsaturated aldehydes and ketones to form silyloxydienes **30** and **31** (Scheme 4.4). These reactive dienes were then trapped with dienophiles and the Diels–Alder adducts were electrophilically cleaved with a solution of TFA.

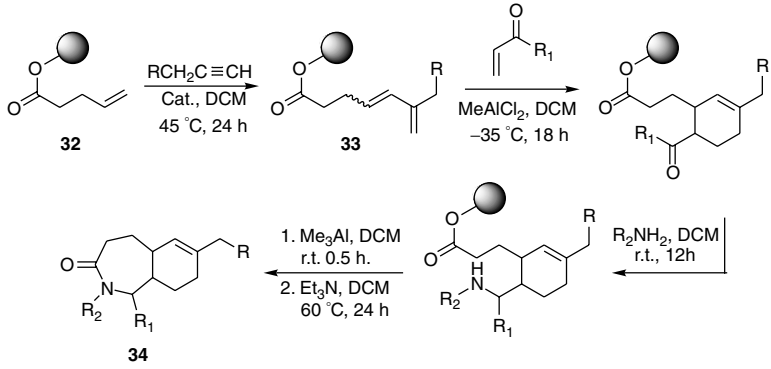


R_1, R_2, R_3 = H, Me, Et, Ar

Scheme 4.4

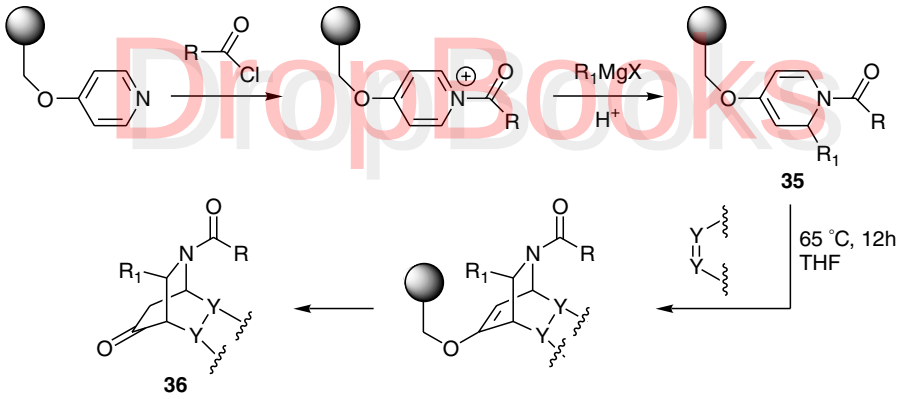
A cross-coupling reactions of terminal alkynes with terminal alkenes **32** supported on Merrifield-resin (Scheme 4.5) in the presence of Grubs' ruthenium initiator $[Cl_2(PCy_3)_2Ru = CHPh]$ provided efficient access to supported 1,3-dienes **33** which were transformed into octahydrobenzazepinones **34** via $MeAlCl_2$ catalyzed Diels–Alder reaction [27].

To generate molecular libraries, a series of 5-oxo-2-azabicyclo[2.2.2]octane and triaza analogs were prepared via a stereospecific Diels–Alder reaction by reacting Wang-resin-bound diene **35** with a variety of dienophiles [28]. After removing the solid support with a strong acid, adducts **36** were isolated; examples of reactions that have furnished the best yields are reported in Scheme 4.6.



R = $(CH_2)_4Me$, CH_2OH, OCH_2Ph, NMeCbz
R_1 = H, Me
R_2 = Me, $(CH_2)_nPh$ n = 1, 2, 3

Scheme 4.5



R	R_1	Dienophile	Yield (%)
p-Me-C_6H_4	*p*-Me-C_6H_4	NPM[a]	52
m-MeO-C_6H_4	*p*-Me-C_6H_4	NPM[a]	61
p-Me-C_6H_4	*p*-Me-C_6H_4	$(EtOCON=)_2$	83

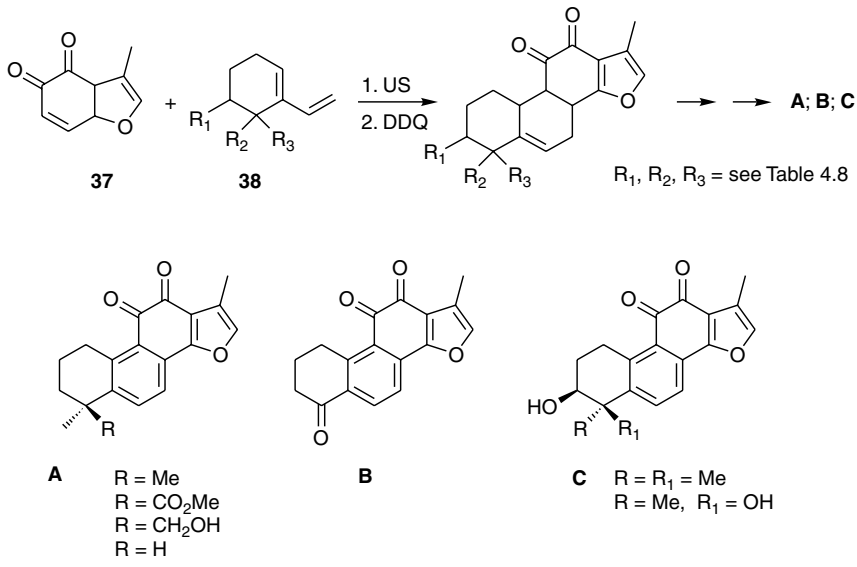
[a] NPM = N-phenylmaleimide.

Scheme 4.6

DropBooks

4.2 ULTRASOUND-ASSISTED DIELS–ALDER REACTION

The use of ultrasonic (US) radiation (typical range 20 to 850 kHz) to accelerate Diels–Alder reactions is undergoing continuous expansion. There is a parallelism between the ultrasonic and high pressure-assisted reactions. Ultrasonic radiations induce cavitation, that is, the formation and the collapse of microbubbles inside the liquid phase which is accompanied by the local generation of high temperature and high pressure [29]. Snyder and coworkers [30] published the first ultrasound-assisted Diels–Alder reactions that involved the cycloadditions of *o*-quinone **37** with appropriate dienes **38** to synthesize abietanoid diterpenes **A–C** (Scheme 4.7) isolated from the traditional Chinese medicine, Dan Shen, prepared from the roots of *Salvia miltiorrhiza* Bunge.

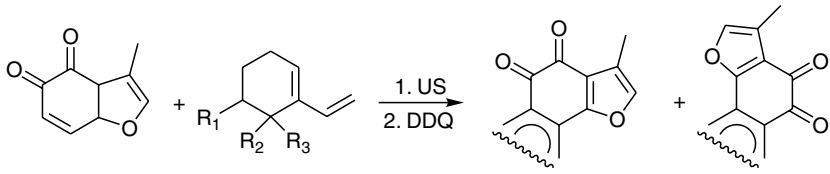


Scheme 4.7

The thermal instability of **37** reduces its applicability with poorly reactive dienes such as vinylcyclohexene and its derivatives **38**, unless high pressure (HP) is employed. Ultrasound is not only effective in promoting the cycloaddition of **37** with **38**, but sometimes also improves the regioselectivity. Some data are illustrated in Table 4.8 and compared with cycloadditions in refluxing benzene and under high pressure. The reactions of **37** with reactive dienes such as cyclopentadiene and 1-(trimethylsiloxy)-1,3-butadiene give a good yield of type **D** adducts under mild conditions, while with less reactive dienes, such as isoprene and butadiene, poor results are obtained.

Ultrasound irradiation is particularly beneficial for Diels–Alder reactions of unactivated azadienes because the reaction can be carried out under mild conditions.

Table 4.8 *o*-Quinone ultrasound-assisted Diels–Alder reactions



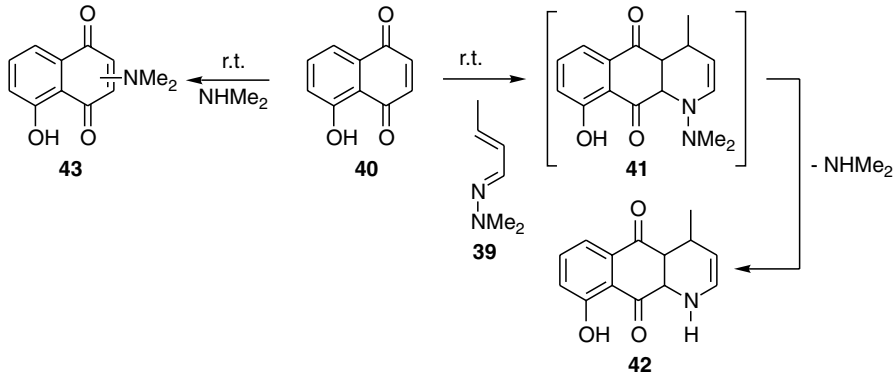
37 **38** **D** **E**

				Yield (%)			**D/E**		
	R_1	R_2	R_3	PhH[a]	HP[b]	US[c]	PhH	HP	US
1	H	H	H	45	67	65	2	6	3.5
2	H	H	Me	11		56	10		20
3	H	H	$SiMe_3$	18	62	57	0.3	0.3	0.2
4	H	Me	Me	53		76	1.2		3.3
5	H	O-COPh	CO_2Me			76[d]			2.5[e]
6	H	O-CMe_2OCH_2				72[f]			4[f]
7	H	O-$(CH_2)_2$-O		18	75	65	1	2.5	8
8	H	CO_2Me	Me			66			8
9	H	OSMDTB	Me			71[g]			12[g]
10	O-CH_2-O		Me	15	73	66	1	7	5
11	OSMDTB	Me	Me			73[h]			30[h]

[a] Reflux, 6–12 h;
[b] 10–11 kbar, 0.75–2 h;
[c] Neat, 45 °C, 2 h;
[d] At 8 °C;
[e] In MeOH, 0 °C, 8 h, yield 50%, **A/B** = 5.5;
[f] At 25 °C; in MeOH, 3 h, yield 59 %, **A/B** =10;
[g] In MeOH, 45 °C, 1.5 h; *h*: In MeOH, 35 °C, 1 h

DropBooks

The Diels–Alder reaction between 1-dimethylamino-4-methyl-1-azadiene **39** and 5-hydroxynaphthoquinone **40** was investigated by Luche, Jenner and coworkers [31] in order to obtain some functionalized derivatives of naturally occurring 4-methylated-1-azaanthraquinones. The reactions were performed under sonochemical, thermal and HP conditions in solution and neat conditions. Some results are illustrated in Scheme 4.8. The primary adduct **41** was not isolated due to a rapid elimination of dimethylamine, and the adduct **42** was obtained as a single regioisomer. Ultrasonic irradiation in PhMe accelerated the Diels–Alder reaction but produced 30 % aminoquinones **43** which is the result of an addition-oxidation of dimethylamine to **40**. Unlike in the Diels–Alder reactions of *o*-quinone **37** with vinylcyclohexenes **38**, methanol and neat reaction conditions were not a good reaction medium for this sonochemical cycloaddition. The study was enlarged to include azanaphthoquinones as dienophiles.



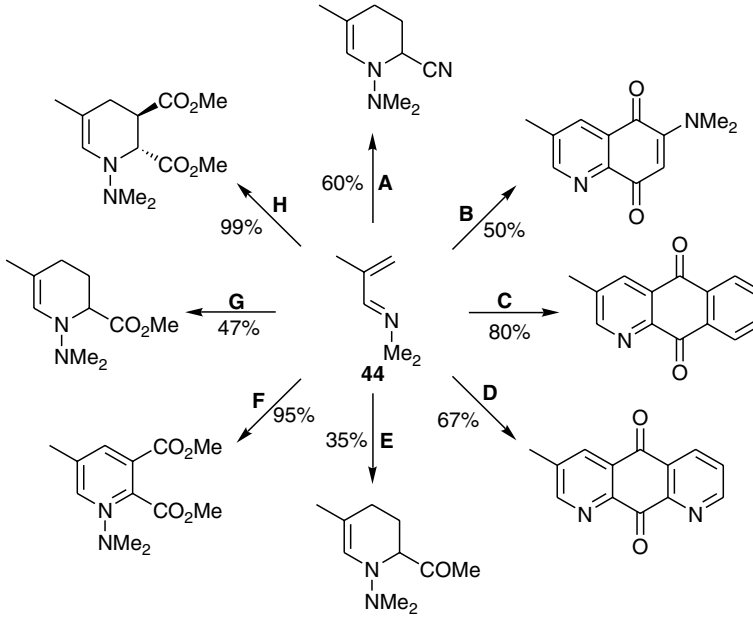
Medium	Conditions	*t*(h)	**42**(%)	**43**(%)
PhMe	US	6	52	30
PhMe	—	24	48	traces
PhMe	HP	6	48	traces
MeOH	US	6	14	traces
MeOH	—	6	15	traces
Neat	US	6	15	traces
Neat	—	6	14	traces

Scheme 4.8

Spanish researchers [32] also noted a considerable improvement upon sonication of Diels–Alder reactions of 1-dimethylamino-3-methyl-1-azadiene **44** with a variety of electron-deficient dienophiles by using diene as solvent or in acetonitrile (Scheme 4.9). Ultrasound irradiation which allows mild reaction conditions gave good to excellent yields.

The sonochemical effect, the importance of solvent and the mechanism of US-assisted Diels–Alder reaction were recently critically investigated [33–35].

Caulier and Reisse [33] studied the influence of US on the yield and diastereoselectivity of the reaction between cyclopentadiene and methyl vinyl ketone in various organic solvents. Yield and *endo/exo* diastereoselectivity increased with US in halogenated solvents ($CHCl_3$, CH_2Cl_2, CH_2Br_2) whereas they were not affected in non-halogenated solvents (CH_3OH, PhMe). The authors give evidence that the cycloaddition is not affected by US, but US promotes the *in situ* generation of hydrogen halide which acts as catalyst. The observed sonochemical effect would be indirect and this would also occur in other cases described in the literature [36]. In many cases the US acts by mechanical effects (the same result could be obtained by very efficient stirring) or by generating radicals or molecules that act as catalysts.



A = Acrylonitrile; **B** = Benzoquinone; **C** = Naphthoquinone; **D** = 5,8-Quinolinequinone; **E** = Methyl vinyl ketone; **F** = Dimethyl acetylene dicarboxylate; **G** = Methyl acrylate; **H** = Dimethyl fumarate

Scheme 4.9

DropBooks

Luche and coworkers [34] investigated the mechanistic aspects of Diels–Alder reactions of anthracene with either 1,4-benzoquinone or maleic anhydride. The cycloaddition of anthracene with maleic anhydride in DCM is slow under US irradiation in the presence or absence of 5% tris (*p*-bromophenyl) aminium hexachloroantimonate (the classical Bauld monoelectronic oxidant, TBPA), whereas the Diels–Alder reaction of 1,4-benzoquinone with anthracene in DCM under US irradiation at 80 °C is slow in the absence of 5% TBPA but proceeds very quickly and with high yield at 25 °C in the presence of TBPA. This last cycloaddition is also strongly accelerated when carried out under stirring solely at 0 °C with 1% $FeCl_3$. The US-promoted Diels–Alder reaction in the presence of TBPA has been justified by hypothesizing a mechanism via radical-cation of diene, which is operative if the electronic affinity of dienophile is not too weak.

The mechanism of cycloaddition reaction of maleic anhydride with anthracene promoted by US irradiation has been the subject of many controversies [32, 37]. Recent work of Da Cunha and Garrigues [35] shows that the reaction proceeds in toluene solution in the 60–85 °C temperature range in 6–3 h,

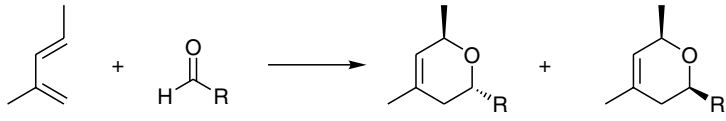
respectively, with high yields (80–88 %) under US irradiation, and that the presence of TBPA does not affect the course of the reaction. Based on these findings the mechanism is postulated to be concerted, excluding any electronic effect.

4.3 MICROWAVE-ASSISTED DIELS–ALDER REACTION

Microwave-assisted Diels–Alder reactions have been performed in solvents [38, 39], in free solvent conditions [38c, 40], in solid phase [39, 41] and in the presence of Lewis acids [38c]. Sometimes some of these reaction conditions were combined.

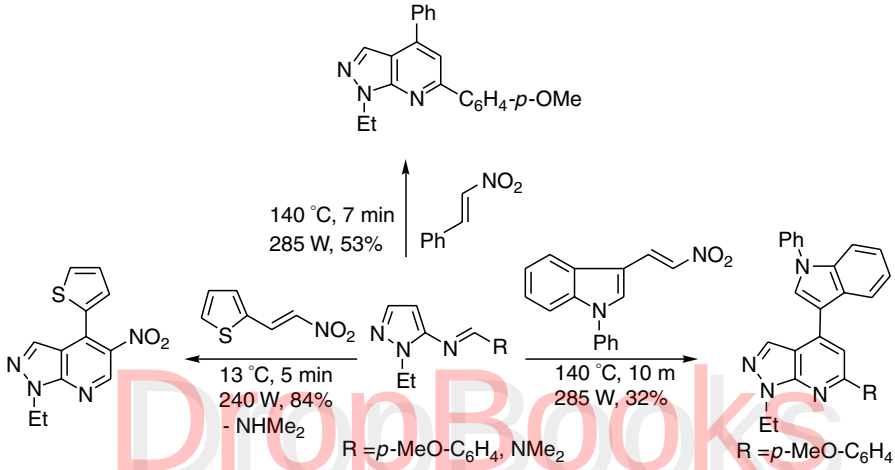
French researchers [38c] have investigated the *hetero*-Diels–Alder reaction of methylglyoxylate and glyoxal monoacetal with 2-methyl-1,3-pentadiene in a microwave oven under various reaction conditions (Table 4.9). The microwave (MW) irradiation does not affect the diastereoisomeric ratio of adducts (*trans/cis* = 70:30) but dramatically reduces the reaction time. The glyoxal monoacetal, for instance, gives 82 % adducts after 5 minutes when submitted to irradiation with an incident power (IP) of 600 W in PhH and in the presence of $ZnCl_2$ (Table 4.9, entry 1), while no reaction occurs if carried out for 4 h at 140 °C in sole PhH. Similarly, methylgloxylate in water at 140 °C gives 82 % adducts after 3 h, whereas microwave irradiation reduces the reaction time to 8 minutes (Table 4.9, entry 5).

Table 4.9 Diels–Alder reactions of glyoxal derivatives promoted by microwaves under different experimental conditions



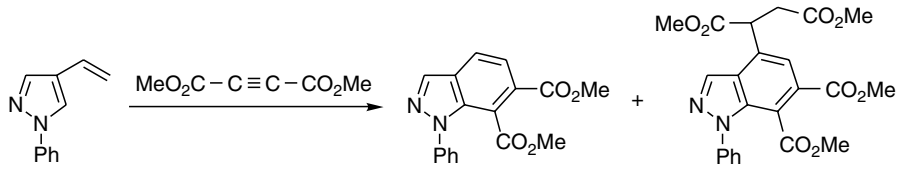
Entry	R	Solvent Cat.	MW (IP.W)	*t* (min)	Yield (%)
1	$CH(OMe)_2$	PhH, $ZnCl_2$	600	5	82
2	$CH(OMe)_2$	H_2O	600	15	76
3	$CH(OMe)_2$	neat	600	15	54
4	CO_2Me	neat	72	10	96
5	CO_2Me	H_2O	72	8	80

A great acceleration was also observed in the cycloadditions of alkylidene derivatives of 5-iminopyrazoles with nitroalkenes, as electron-poor dienophiles, under MW-irradiation in solvent-free conditions [40c]. Some results are illustrated in Scheme 4.10. All the reactions took place with loss of HNO_2 and/or $NHMe_2$ after the cycloaddition, inducing aromatization of the final product.

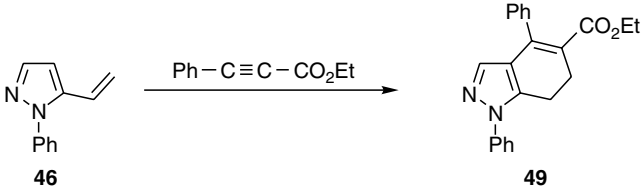


Scheme 4.10

Diels–Alder reactions of vinylpyrazoles **45** and **46** only occur with highly reactive dienophiles under severe conditions (8–10 atm, 120–140 °C, several days). MW irradiation in solvent-free conditions also has a beneficial effect [40b] on the reaction time (Scheme 4.11). The indazole **48**, present in large amounts in the cycloaddition of **45** with dimethylacetylenedicarboxylate, is the result of an ene reaction of primary Diels–Alder adduct with a second molecule of dienophile followed by two [1,3]-sigmatropic hydrogen shifts [42]. The MW-assisted cycloaddition of **46** with the poorly reactive dienophile ethylphenyl-propiolate (Scheme 4.11) is significant; under the classical thermal reaction conditions (140 °C, 6 d) only polymerization or decomposition products were detected.



Reaction conditions	Products (Yield %)
1. DCM, 150 °C, 8–10 atm	**47** + **48** (18 %)
2. MW, 780 W, 130 °C, 6 min	**47** (10 %) + **48** (62%)



Reaction conditions	Product (Yield %)
1. 140 °C, 6 d	0
2. MW, 180 W, 180 °C, 15 min	19

Scheme 4.11

The Diels–Alder reaction of anthracene and maleic anhydride gives 90 % adduct in refluxing dioxane for 60 h [43]. MW irradiation of free-solvent reaction in a commercial microwave oven (2450 MHz) gives the same yield, but the reaction time is reduced to 3 minutes [40a]. The free-solvent reaction was also investigated by using graphite powder as support [39a]: a continuous MW irradiation with an IP of 120 W during 1 minute gave traces of adduct, but with 30 W and a sequential irradiation (irradiation with 'battlements'), the adduct was isolated with 75 % yield. This and other MW-assisted Diels–Alder reactions supported on graphite are illustrated in Table 4.10. Graphite is responsible for a high-temperature gradient leading to increased reaction rates when compared with conventional procedures which use a solvent. The same process was applied to cycloadditions involving carbonyl derivatives as dienophiles and 2,3-dimethyl-1,3-butadiene as diene [39b] (Scheme 4.12). The cycloadditions were

Table 4.10 Microwave-assisted Diels–Alder reactions supported on graphite

Reagents	T_{max} (°C)	t(min)	MW (IP)	Yield (%)
A[a] + DEF[b]	370	1	120	92
A + MA[c]	155	1 × 3	30	75
A + DAD[d]	130	1 × 3	30	97
44 + DAD	*e*	1 × 10	30	50

[a] Anthracene;
[b] Diethylfumarate;
[c] Maleic anhydride;
[d] Dimethyl acetylenedicarboxylate;
[e] Not indicated

dramatically accelerated with respect to conventional heating conditions, and the absorption of the reagents on graphite allowed the reactions to be carried out in an open reactor.

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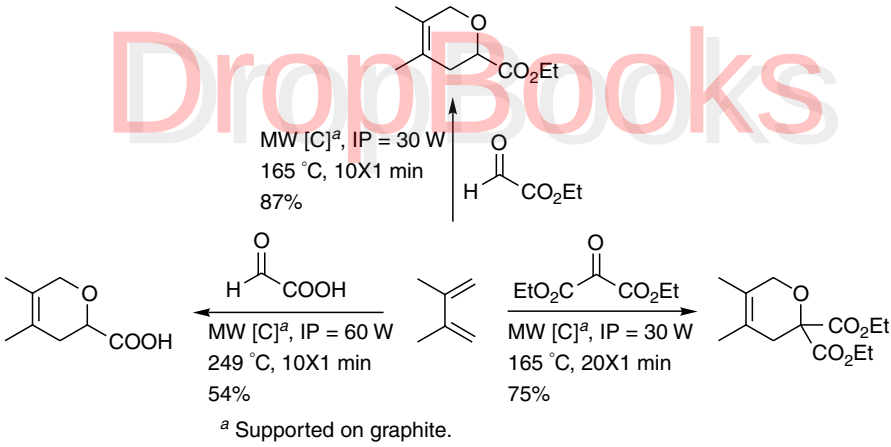
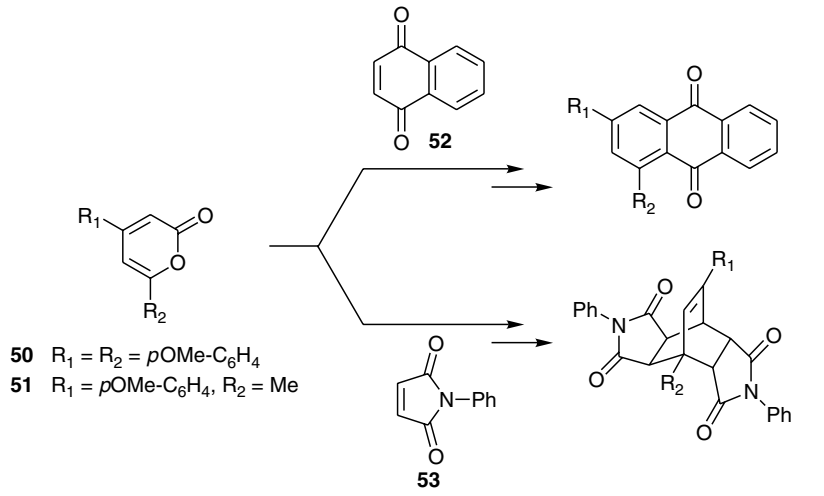


Scheme 4.12

A broad study on the MW-assisted Diels–Alder reactions of 2H-pyran-2-ones **50** and **51** with 1,4-naphthoquinone **52** and N-phenylmaleimide **53** (Equations 4.3) supported on silica-gel, K-10 montmorillonite, fitrol and alumina was carried out by Samant and colleagues [41].



(4.3)

The results of reactions with and without MW irradiation are reported in Table 4.11. The reaction yields are comparable, but the reaction times of the irradiated reactions are considerably reduced. The alumina does not give acceptable results. The same reactions were carried out in nitrobenzene as solvent and under free-solvent conditions with and without MW irradiation. The results are reported in Table 4.12. In this case too, the only significant difference is the reaction time, so that the authors [41] concluded that MW-promoted reactions proceed like the thermal reactions except for a much higher reaction rate.

Table 4.11 Diels–Alder reactions of **50** and **51** with **52** and **53** in the presence of a solid support

Reagents	Support	MW[a] (Yield %)	NO-MW[b] (Yield %)
50 + **52**	SiO_2	73	70[c]
51 + **52**	SiO_2	68	76[c]
50 + **53**	SiO_2	68	68[c]
51 + **53**	SiO_2	68	70[c]
50 + **52**	K-10	65	66[d]
51 + **52**	K-10	66	69[d]
50 + **53**	K-10	67	66[d]
51 + **53**	K-10	68	68[d]
50 + **52**	Fitrol	69	67[c]
51 + **52**	Fitrol	70	69[c]
50 + **53**	Fitrol	72	68[c]
51 + **53**	Fitrol	73	69[c]

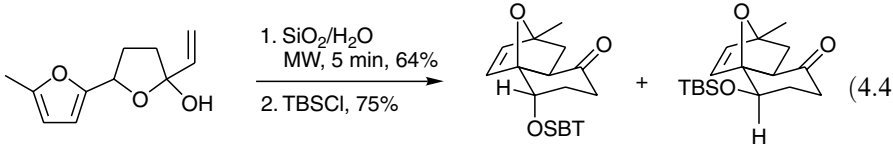
[a] With MW, 4 min, HPL 80 % power level;
[b] Without MW, 4 h;
[c] At 120 °C;
[d] At 140 °C

Table 4.12 Diels–Alder reactions of **50** and **51** with **52** and **53** under various conditions

	Free solvent Yield (%)		Nitrobenzene Yield (%)	
Reagents	MW[a]	NO-MW[b]	MW[a]	NO-MW[b]
50 + **52**	53	48	76	82
51 + **52**	51	69	74	74
50 + **53**	49	55	71	65
51 + **53**	50	58	70	61

[a] With MW, 4 min, HPL 80 % power level;
[b] Without MW, 4 h, 210 °C

An example of intramolecular MW-assisted Diels–Alder reaction is illustrated in Equation 4.4.



(4.4)

54 **55** **56**

The hemiacetal **54** adsorbed on water-saturated silica gel gives, by MW irradiation, a 1:1 mixture of cycloadducts isolated as silyl derivatives **55** and **56**. The water is probably necessary for the success of the reaction because (i) it is an efficient generator of heat in the MW process, (ii) it accelerates the cycloaddition by hydrophobic effect, and (iii) it facilitates the hemiacetal–hydroxyketone equilibrium which furnishes the dienophile moiety for the cycloaddition [42].

DropBooks

4.4 PHOTO-INDUCED DIELS–ALDER REACTION

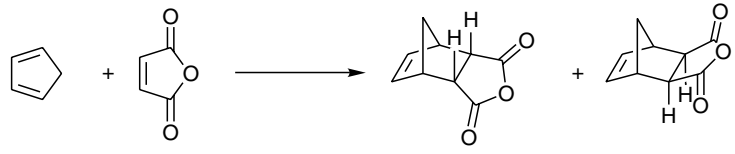
Photo-induced Diels–Alder reaction occurs either by direct photo activation of a diene or dienophile or by irradiation of a photosensitizer (Rose Bengal, Methylene Blue, hematoporphyrin, tetraphenylporphyrin) that interacts with diene or dienophile. These processes produce an electronically excited reagent (energy transfer) or a radical cation (electron transfer) or a radical (hydrogen abstraction) that is subsequently trapped by the other reagent.

The single-electron transfer from one excited component to the other component acceptor, as the critical step prior to cycloaddition of photo-induced Diels–Alder reactions, has been demonstrated [43] for the reaction of anthracene with maleic anhydride and various maleimides carried out in chloroform under irradiation by a medium-pressure mercury lamp (500 W). The (singlet) excited anthracene ($^1AN^{\bullet}$), generated by the actinic light, is quenched by dienophile

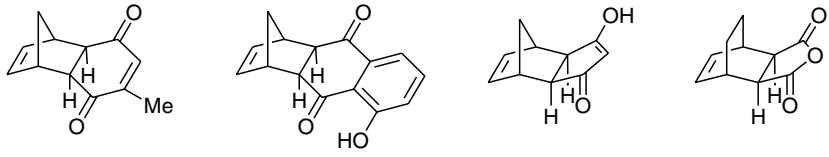
(DP) and leads (Equation 4.5) to the formation of an anthracene cation radical as a result of the single-electron transfer process. The resulting ion-radical pair $[AN^{\bullet+}, DP^{\bullet-}$ is the critical intermediate that subsequently evolves to cycloadduct (AD).

$$^1AN^{\bullet} + DP \longrightarrow \left[AN^{\bullet+}, DP^{\bullet-}\right] \longrightarrow AD \qquad (4.5)$$

The thermal reaction of cyclopentadiene **(1)** with maleic anhydride gives 98 % kinetically favoured *endo* adduct, unless the mixture is heated for a long time [44]. Under photolysis conditions and in the presence of triethylamine in dry ethanol, a reversed selectivity was found [45] (Scheme 4.13).



Conditions	*endo/exo*
Et_2O, r.t., very fast	98:2
EtOH, Et_3N, hν (300 nm), r.t., 6 h	2:98



hν, Et_3N (5 %) Yield : 64%

hν, Et_3N (50%) Yield : 81%

hν, Et_3N (20 %) Yield : 70%

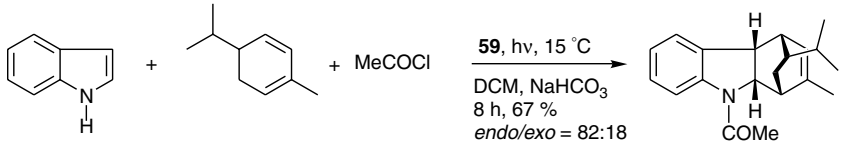
hν, Et_3N (5%) Yield : 90%

Scheme 4.13

The photo-induced *exo* selectivity was observed in other classic Diels–Alder reactions. Data relating to some *exo* adducts obtained by reacting cyclopentadiene or cyclohexadiene with 2-methyl-1,4-benzoquinone, 5-hydroxynaphthoquinone, 4-cyclopentene-1,3-dione and maleic anhydride are given in Scheme 4.13. The presence and amount of Et_3N plays a decisive role in reversing the *endo* selectivity. The possibility that the prevalence of *exo* adduct is due to isomerization of *endo* adduct under photolytic conditions was rejected by control experiments, at least for less reactive dienophiles.

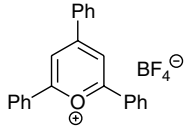
Indole is a weak dienophile in normal Diels–Alder reactions and must be activated by electron-withdrawing substituents at C-2 and C-3. High

temperatures and long reaction times are necessary in any case. In contrast, indole gives cycloaddition with electron-rich dienes under mild conditions by a photo-induced electron transfer reaction [46]. Thus by irradiation of the indole **57**, the diene **58** and the sensitizer **59** in the presence of acetyl chloride, the cycloadduct **60** was obtained in 67% yield after 8 h (Equation 4.6).



57 58 60

(4.6)



59

Acetylchloride is a trapping agent that allows the reaction to go completion, transforming the product into a less oxidizable compound.The results of other reactions between indole **(57)** and substituted cyclohexa-1,3-dienes show that the photo-induced Diels–Alder reaction is almost completely regioselective. In the absence of **59** the cycloaddition did not occur; the presence of [2+2] adducts was never detected. Experimental data support the mechanism illustrated in Scheme 4.14. The intermediate **57a**, originated from bond formation between the indole cation radical and **58**, undergoes a back-electron transfer to form the adduct **60** trapped by acetyl chloride.

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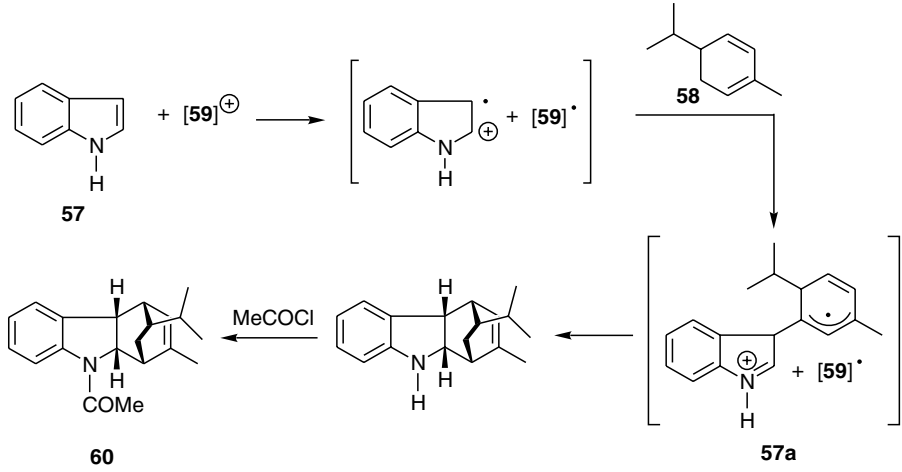


60 57a

Scheme 4.14

The investigation was recently enlarged to include functionalized exocyclic dienes **61–63** (Figure 4.2) which are promising starting materials for the synthesis of carbazole derivatives [47]. Some significant results from the photocycloadditions with 5-substituted indoles **64** catalyzed by **59** and **65** (Figure 4.2) are reported in Table 4.13. *cis*-Bridged adducts were always obtained with high regioselectivity; with **62** and **63** a 1:1 mixture of diastereoisomers with the stereogenic centers bearing the phenyl group were obtained.

The cycloaddition of photoenol of *o*-methylbenzaldehyde **66** with 5-alkylidene-1,3-dioxane-4,6-dione derivatives **67** is an example of a photo-induced Diels–Alder reaction in which one component, the diene in this case, is generated by irradiation [48]. The yields of some cycloadducts **68**, generated by photo-irradiation of a benzene solution of **66** and **67** at room temperature, are reported in Table 4.14. The first step of the reaction is the formation of (E)-enol **69** and (Z)-enol **70** (Equation 4.7) by an intramolecular hydrogen abstraction of **66** followed by a stereo- and regioselective cycloaddition with

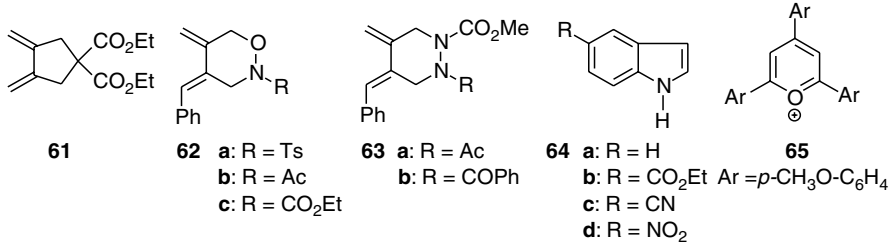
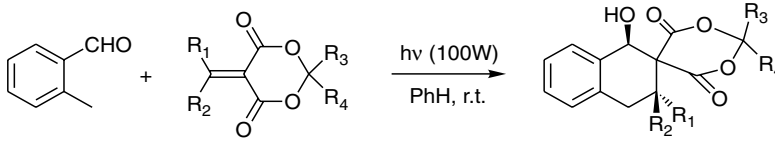


Figure 4.2

Table 4.13 Photoinduced Diels–Alder reactions of indoles **64** and dienes **61–63** with sensitizers **59** and **65**

Indole	Diene	Sensitizer	Yield (%)
64b	**61**	**59**	61
64d	**61**	**65**	80
64b	**62a**	**59**	50
64c	**62a**	**59**	61
64d	**62b**	**65**	63
64d	**62c**	**65**	60
64d	**63a**	**65**	58

Table 4.14 Diels–Alder reactions of photoenol of **66** with **67**



66 **67** **68**

Entry	R_1	R_2	R_3	R_4	*t*(h)	Yield (%)
1	*i*-Pr	H	Me	Me	3	80
2	$-(CH_2)_5-$		Me	Me	2	53
3	Cy	H	Me	Me	3	62
4	*i*-Pr	H	$-(CH_2)_4-$		2	54
5	$-(CH_2)_5-$		$-(CH_2)_4-$		2	69
6	$-(CH_2)_5-$		$-(CH_2)_5-$		3	65

67. Stereochemical analysis shows that the adducts of entries 1, 3 and 6 in Table 4.14 are derived by an *exo*-approach of **69** with their respective dienophiles.

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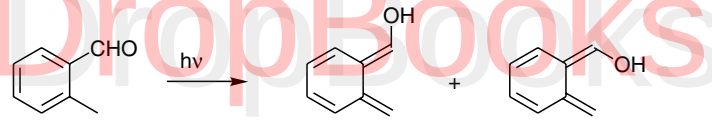
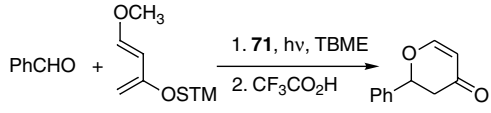


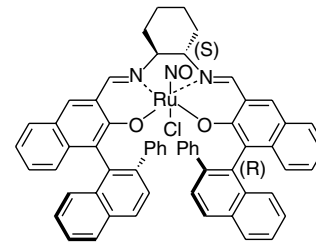
(4.7)

66 **69** **70**

The coupling photolysis–Lewis acid is also sometimes effective in promoting a Diels–Alder reaction. Thus, cationic (R,S)-(ON)Ru-salen homochiral complex **71** catalyzed the Diels–Alder reaction between Danishefsky's diene and benzaldehyde when the reagents were exposed to direct sunlight through a window or to incandescent light in *t*-butyl methyl ether (TBME)[49] (Equation 4.8). The reaction in the dark was very slow and only 3 % *ee* was detected.



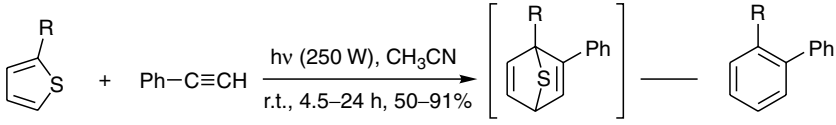
hv	*T* (°C)	*t* (d)	Yield (%)	ee (%)
sunlight	r.t.	7	54	79
60 W	0	2	26	83



(4.8)

71

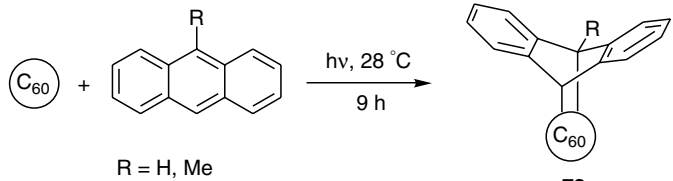
As shown above, a high regioselectivity is a characteristic of photo-induced Diels–Alder reactions. A further example is the photochemical reaction between 2-electron-withdrawing substituted thiophenes and phenylacetylene; when the reactants were irradiated in acetonitrile, *ortho*-substituted biphenyls were obtained [50] (Equation 4.9). When sensitizers were used no biphenyl adduct was observed. It was suggested that the reaction occurs via triplet excited thiophene derivative which gives a radical intermediate by reacting with phenylacetylene; this intermediate can undergo ring-closure directly to phenyl with sulfur elimination or lead to 1,4-cycloaddition adduct with successive sulfur extrusion.



(4.9)

R = NO_2, COMe, CHO

The low solubility of fullerene (C_{60}) in common organic solvents such as THF, MeCN and DCM interferes with its functionalization, which is a key step for its synthetic applications. Solid state photochemistry is a powerful strategy for overcoming this difficulty. Thus a 1:1 mixture of C_{60} and 9-methylanthracene (Equation 4.10, R = Me) exposed to a high-pressure mercury lamp gives the adduct **72** (R = Me) with 68% conversion [51]. No 9-methylanthracene dimers were detected. Anthracene does not react with C_{60} under these conditions; this has been correlated to its ionization potential which is lower than that of the 9-methyl derivative. This suggests that the Diels–Alder reaction proceeds via photo-induced electron transfer from 9-methylanthracene to the triplet excited state of C_{60}.



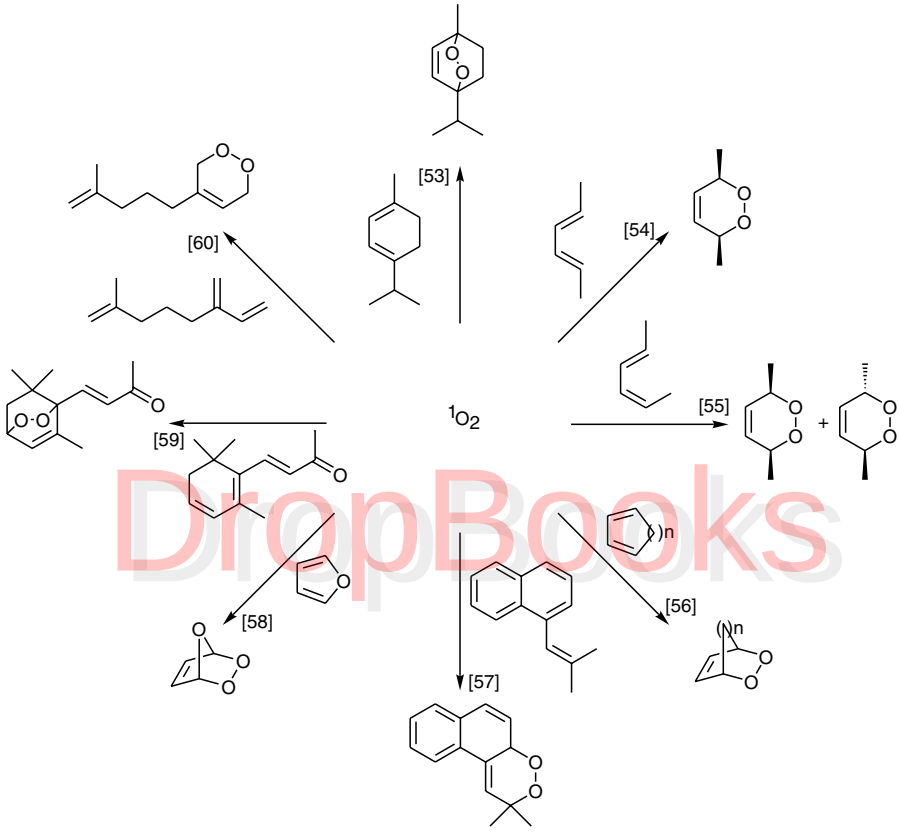
R = H, Me

72

(4.10)

The photo-oxygenation of 1,3-dienes by singlet oxygen [52] gives peroxides which, especially those of an aromatic type, release oxygen upon cycloreversion and therefore are a form of chemically stored singlet excited oxygen molecules. The photooxygenation is carried out in the presence of sensitizers such as Rose

Bengal, Methylene Blue, haematoporphyrin and tetraphenylporphyrin and, generally, in organic solvents. Some examples are illustrated in Scheme 4.15. Peroxide products obtained from fatty acid precursors [61] or from cyclopentadienes [62] are of interest as pharmaceuticals or for biomedical studies; others are versatile starting materials for further transformation.



Scheme 4.15

The primary interaction of singlet oxygen, produced by energy transfer from the excited sensitizer, with the diene can give rise to an exciplet that then collapses to peroxide, to a 1,4-biradical or to a 1,4-zwitterion; alternatively, the adduct is the result of a concerted action without the involvement of an intermediate. Detailed kinetic Diels–Alder investigations of singlet oxygen and furans indicate that the reactions proceed concertedly but are asynchronous with the involvement of an exciplex as the primary reaction intermediate [63].

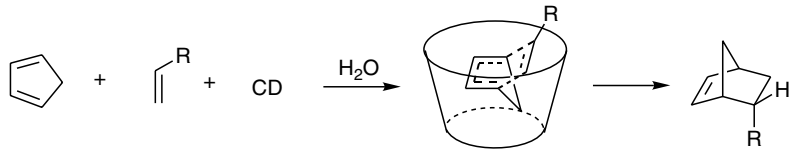
4.5 DIELS–ALDER REACTION IN MOLECULAR CAVITIES

The transition state of concerted Diels–Alder reactions has stringent regio- and stereochemical requirements and can assume settled configurations if the reaction is carried out in a molecular cavity. Cyclodextrins, porphyrin derivatives and cyclophanes are the supramolecular systems that have been most investigated.

Cyclodextrins (CDs) are cyclic α-1,4-linked D-(+)-glucopyranose units (α-CD = six units; β-CD = seven units) that form inclusion complexes with a variety of hydrophobic molecules in aqueous medium [64].

The CDs serve the as the reaction vessel, and the aggregation of the reagents within the cavity can enhance the reactivity and selectivity of the process. There are many examples of CD-facilitated Diels–Alder reactions [65].

The Diels–Alder reactions of cyclopentadiene with methyl vinyl ketone and acrylonitrile are accelerated when carried out in water in the presence of β-CD but are slower with α-CD [65a] (Scheme 4.16). This is in agreement with the observation that the transition states of these cycloadditions fit into the hydrophobic cavity of β-CD but not in the smaller α-CD cavity.



R	T(°C)	$k_{\alpha-CD}/k^a$	$k_{\beta-CD}/k^a$
COMe	20	0.6	2.5>
CN	30	0.8	9.0

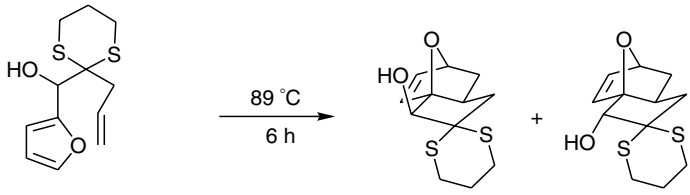
[a] Relative second-order rate constants of reactions performed in water in the presence and absence of CD.

Scheme 4.16

The importance of the relationship between the macrocycle cavity and the binding of two reagents is shown by the cycloadditions of cyclopentadiene with diethyl fumarate and ethyl acrylate in aqueous solution. The presence of β-CD strongly accelerates the first cycloaddition, while it slows down the reaction rate of the second, probably because the cavity favors the binding of two molecules of either diene or dienophile [65c].

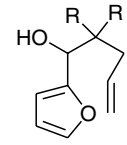
Intramolecular Diels–Alder reactions employing furan as the diene component are an effective step in the synthesis of many natural products, but difficulties are sometimes encountered due to the poor dienic character of the aromatic ring. Using CDs can help to overcome this problem. Thus, when **73** is heated in water at 89 °C for only 6 h a 20% epimeric 1:2 mixture of **74** and **75** is

formed [65b] (Scheme 4.17), while in the presence of 1 eq. of β-CD, 91 % of the adducts are obtained. No significant yield enhancement was observed when α-CD was employed. The analogous compounds **76** and **77** did not show any tendency to cyclize under these conditions.



73 **74** **75**

Medium	**74/75**	Yield (%)
H_2O	1:2	20
H_2O + α-CD		25
H_2O + β-CD	1:1.5	91

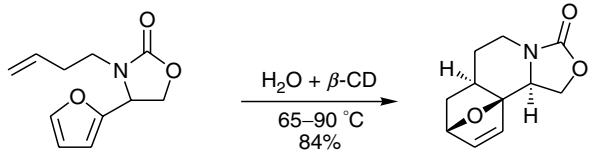


76 R = Me
77 R = OEt

Scheme 4.17

DropBooks

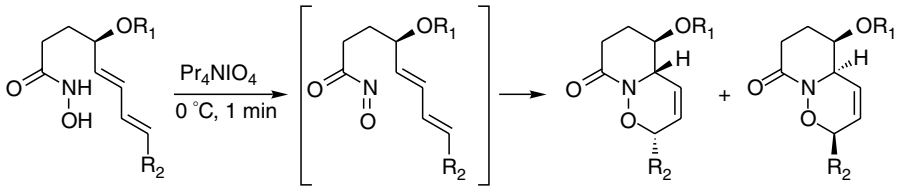
The intramolecular Diels–Alder reaction of **78** was investigated during the synthesis of isoquinoline alkaloids [65i]. No reaction occurred when solid-phase conditions were used (Florosil in DCM and $CaCl_2$) or when a variety of Lewis acids were employed ($SnCl_4$, BF_3, $RAlCl_2$, $Ti(i-Pr)_4$–$TiCl_4$). A 56 % yield of **79** was obtained by carrying out the cycloaddition in toluene in a sealed tube at 200 °C. β-CD catalysis in water under milder conditions (Equation 4.11) improved the conversion to 84 %.



78 **79** (4.11)

The intramolecular *hetero*-Diels–Alder reactions of 4-O-protected acylnitroso compounds **81**, generated *in situ* from hydroxamic acids **80** by periodate oxidation, were investigated under various conditions in order to obtain the best *endo/exo* ratio of adducts **82** and **83** [65h] (Table 4.15). The *endo* adducts are key intermediates for the synthesis of optically active swainsonine [66a] and pumiliotoxin [66b]. The use of CDs in aqueous medium improves the reaction yield and selectivity with respect to organic solvents.

Table 4.15 Diels–Alder reactions of acylnitroso compounds



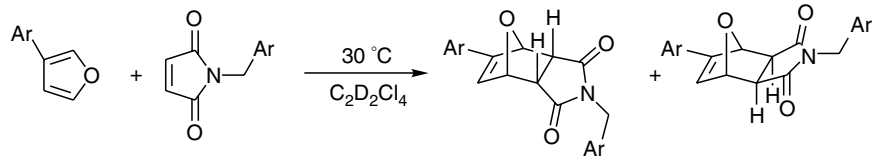
80 **81** **82** (*endo*) **83** (*exo*)

R_1	R_2	Medium	*endo/exo*	Yield (%)
Bn	H	$CHCl_3$	1.3	76
Bn	H	H_2O	4.1	87
Bn	H	$H_2O + \beta$CD	2.8	93
Bn	H	$H_2O + \gamma$CD	1.7	86
MOM	H	H_2O	4.4	93
MOM	H	$H_2O + \beta$CD	3.1	91
MOM	H	$H_2O + \gamma$CD	3.4	74
Bn	Et[a]	H_2O-DMSO	4.2	77
Bn	Et	H_2O-DMSO[b] $+ \alpha$CD	4.1	80
Bn	Et	H_2O-DMSO[b] $+ \beta$CD	2.7	75

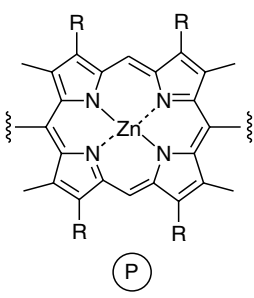
[a] Oxidation with $NaIO_4$
[b] H_2O-DMSO = 5 : 1.

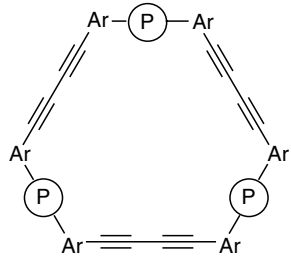
As an approach to biomimetic catalysis, Sanders and colleagues [67] synthesized a series of 1,1,2-linked cyclic porphyrin trimers that allow the stereo- and regiochemistry of the Diels–Alder reaction of **84** and **85** within the molecular cavity to be controlled, thereby producing prevalently or exclusively the *endo* **86** or the *exo* **87** adduct. Two examples are illustrated in Scheme 4.18. At 30 °C and in the absence of **88**, the reaction furnishes a mixture of diastereoisomers, while the addition of one equivalent of trimer **88** accelerates the reaction 1000-fold and the thermodynamically more stable *exo* adduct **87** is the sole detectable product.

In contrast, the trimer **89** with ethyne and butadiyne links stabilizes the thermodynamically disfavored *endo* transition state, and the *endo* adduct **86** is rapidly and almost exclusively formed.



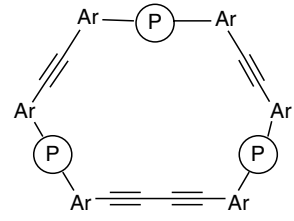
84 **85** **86** (*endo*) **87** (*exo*)





88

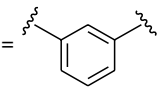
R = Et



89

R = $CH_2CH_2CO_2Me$

Ar =



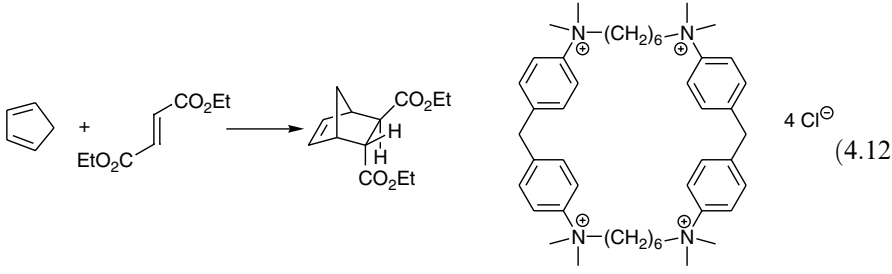
Host	Selectivity	k_{rel} (*endo*)[a]	k_{rel} (*exo*)[a]
none	exo + endo		
88	exo		1000
89	endo	500	

[a]Relative to rates in the absence of host at 30 °C.

DropBooks

Scheme 4.18

An example of a cyclophane-type cavity is the azacyclophane CP66 supramolecular system which provides a lipophilic cavity with an internal width of approximately 6.5 Å, as well as positive charges which accelerate and increase the selectivity of the process. The Diels–Alder reaction of cyclopentadiene with diethylfumarate at 20 °C in 10 % and 50 % dioxane–water is accelerated by the presence of CP66 by 2.9 and 1.5 times, respectively [65c] (Equation 4.12).



(4.12)

[CP 66]

4.6 MICELLE-PROMOTED DIELS–ALDER REACTION

Micellar medium has received great attention because it solubilizes, concentrates and orientates the reactants within the micelle core and in this way accelerates the reaction and favors the regio- and stereoselectivity of the process [68]. In addition the micellar medium is cheap, can be reused, is more versatile than cyclodextrins and more robust than enzymes. With regard to Diels–Alder reactions, we may distinguish between (i) those in which one or both reagents are surfactants which make up the micellar medium, and (ii) those that are carried out in a micellar medium prepared by a suitable surfactant.

4.6.1 Diels–Alder Reactions of Surfactant Reagents

One of the first examples of Diels–Alder reactions of surfactant reagents was reported by Keana [69].

The surfactant dienes **90** and **91** (Figure 4.3), analogs to commercially available sodium dodecyl sulfate (SDS) and dodecyl maltoside, react rapidly with highly hydrophilic and reactive triazoline dione **92** in water at 25 °C forming, quantitatively, the corresponding adducts. The Diels–Alder reactions with less potent dienophile **93** gave, similarly, quantitative yields in 0.5 h and 3 h with **90** and **91**, respectively.

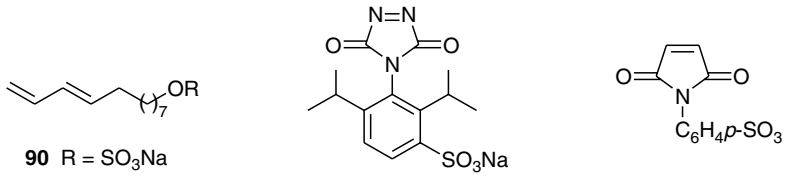
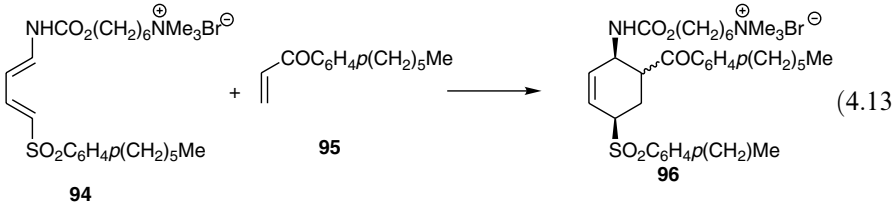


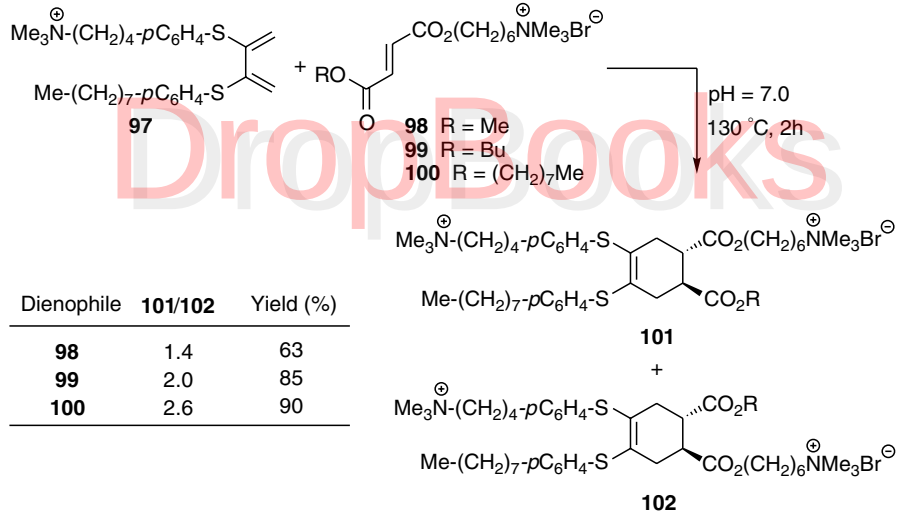
Figure 4.3

Jaeger and coworkers investigated the ability of aqueous surfactant aggregates to control the regiochemistry of Diels–Alder reaction of a surfactant 1,3-diene with a surfactant dienophile [70]. Surfactant 1,3-diene **94** reacts with dienophile **95**, giving a mixture of *endo/exo* adducts **96** whose regiochemistry is the opposite of that expected if the reagents had reacted in their preferred orientation within the mixed micelle. This demonstrates the importance of orientational effects in the aggregates [70a] (Equation 4.13).



(4.13)

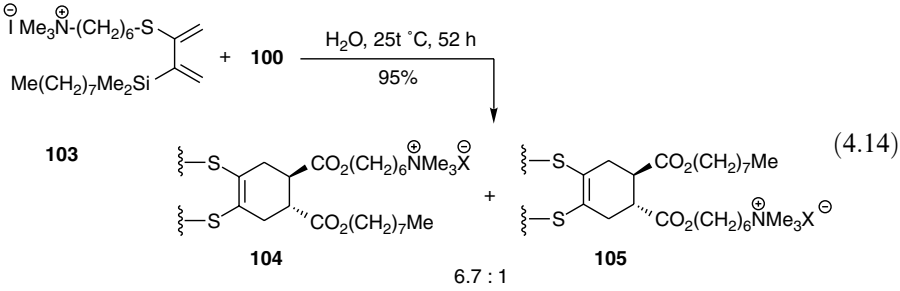
The substituents at C-2, C-3 within diene **97** and those at C-1, C-2 within dienophiles **98–100** are electronically and/or sterically equivalent with respect to diene and dienophile reaction centers, respectively, and therefore cycloaddition should not display regiochemical bias in the absence of orientational effects. The Diels–Alder reactions of **97** prepared *in situ* with **98–100** gave an excess of **101** (Scheme 4.19) [70b], which are the expected regioisomers if the reagents react in their preferred orientations within a mixed micelle with an ammonium head group at the aggregate–water interface and the remainder in the micelle interior.



Dienophile	**101/102**	Yield (%)
98	1.4	63
99	2.0	85
100	2.6	90

Scheme 4.19

A higher regioselectivity was observed [70c] in the cycloaddition in water at 25 °C of diene surfactant **103** with **100** (Equation 4.14, **104/105** = 6.7:1) in agreement with the expectation that the organizational ability of aqueous aggregates is higher at lower temperatures.



(4.14)

Parallel studies on the cycloadditions of non-surfactant dienes **106** and **107** and the dienophile **108** (Figure 4.4), analogs of **97**, **103** and **98–100**, respectively, show that the regioisomer adducts were, in this case, obtained in equal amounts, supporting the idea that orientational effects in micelles promote the regioselectivity of a Diels–Alder reaction of a surfactant diene and a surfactant dienophile.

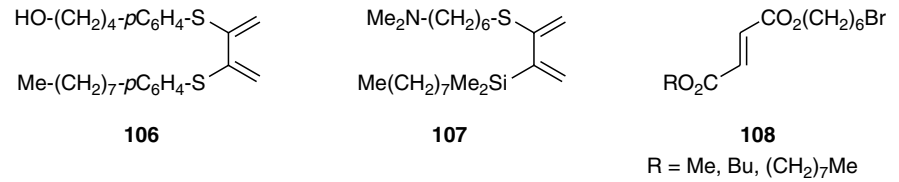


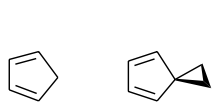
Figure 4.4

4.6.2 Micellar Catalysis

There are few examples of the influence of micelles on reactivity and selectivity of Diels–Alder reactions, and the observed effects are sometimes capricious. Compared to the reaction in pure water, modest [71] and exceptional [72] accelerations and even retardations [65e, g, 73] have been observed, and little [73b, 74] and high [75] *endo/exo* diastereoselectivities were found.

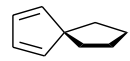
The cycloadditions of cyclopentadiene **1** and its spiro-derivatives **109** and **110** with quinones **52**, **111** and **112** (Scheme 4.20), carried out in water at 30 °C in the presence of 0.5 % mol. of cetyltrimethylammonium bromide (CTAB), gave the *endo* adduct in about 3 h with good yield [72b]. With respect to the thermal Diels–Alder reaction, the great reaction rate enhancement in micellar medium (Scheme 4.20) can be ascribed to the increased concentration of the reactants in the micellar pseudophase where they are also more ordered.

The catalytic activity of micelles bearing catalytically active metal counterions (Lewis acid-surfactant combined catalysts, LASCs) on Diels–Alder reactions was recently investigated [72a, 76].



1

109



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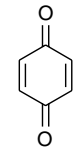
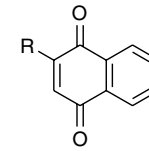


111



52 R = H
112 R = Me

Reagents	MR(Yielsd %)[a]	TR (Yield %)[b]
109+**111**	66	60
110+**111**	78	45
1+**52**	68	50
1+**112**	86	0
109+**52**	75	53
110+**52**	76	62

[a] Micellar reaction (H_2O, CTAB, 30 °C, 3h).
[b] Thermal reaction (PhMe110 °C, 10-12h).

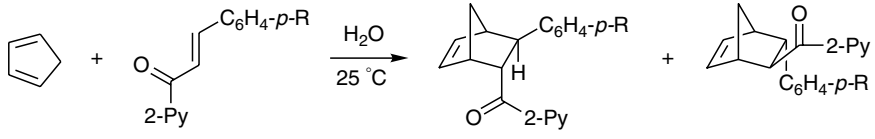
Scheme 4.20

Engberts and coworkers [72a] studied kinetically the influence of micelles of CTAB, SDS, $C_{12}E_7$ and LASCs, such as copper and zinc didodecyl sulfate [$Cu(DS)_2$, $Zn(DS)_2$], on the Diels–Alder reactions of cyclopentadiene with 2-propen-1-ones **113** in aqueous medium at 25 °C. The *endo* adduct was the highly prevalent diastereoisomer. The results are reported in Table 4.16. Classic micelles (SDS, CTAB, $C_{12}E_7$) (Table 4.16, entries 2, 3 and 4) slow the reaction down, presumably because the dienophile probably resides primarily in the aqueous phase where the concentration of diene is reduced due to its partial solubilization by the micelles. The presence of Cu(II) ions accelerates the reaction (entries 6 and 7), but a comparison with the reaction catalyzed by $Cu(NO_3)_2$ only (entry 5) once again shows that micelles of CTAB and $C_{12}E_7$ inhibit cycloaddition. An extraordinary micellar catalysis was found when the reaction was carried out in the presence of $Cu(DS)_2$, that is, when the diene, dienophile and copper ion bind simultaneously to the micelle. Comparing this catalytic effect of the reaction of **1** with **113a** (entry 8: 6243) to that found for the same uncatalyzed reaction in acetonitrile (Chapter 6, Table 6.5: 287), the $Cu(DS)_2$ micelles in water accelerate the reaction of **1** with **113a** by 1.8×10^6 times.

Different results were obtained by Kobayashi and colleagues [76] performing the Diels–Alder reaction of 2,3-dimethyl butadiene with N-butylmaleimide in water in the presence of various dodecyl sulfate (DS) and dodecane sulfonate (DCS) LASCs [$M(DS)_n$: M = Sc, Cu; $n = 3, 2$; $M(DCS)_n$: M = Sc, Yb, Mn, Co, Cu, Zn, Na, Ag; $n = 3, 2, 1$]. Unexpectedly, no acceleration was observed with respect to the reactions carried out in water only, and no catalytic effect was found also by using a bidentate dienophile which, in principle, should be able to coordinate the metal cation in the LASC system.

PROPBOOKS

Table 4.16 Micellar catalysis of Diels–Alder reactions of cyclopentadiene (**1**) with 3-(*p*-substituted phenyl)-1-(2-propen-1-one (**113**) in water at 25 °C. Relative rate constants (k_{rel}) to the reactions performed in sole water



1 **113 a**: R = NO_2 (*endo*) (*exo*)
b: R = CH_2SO_3Na
c: R = $(CH_2NMe_3)Br$
d: R = H

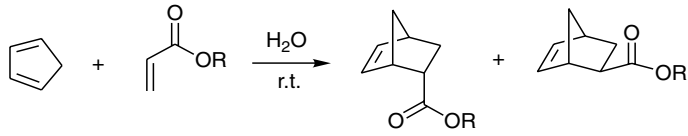
		$k_{rel} = k_{cat}/k_{H_2O}$		
Entry	Catalyst	**113a**	**113b**	**113c**
1	none	1	1	1
2	SDS	0.91	0.83	0.60
3	CTAB	0.90	0.16	0.82
4	$C_{12}E_7$[a]	0.83	0.93	0.84
5	$Cu(NO_3)_2$ (10^{-2} M)	808	793	869
6	CTAB + $Cu(NO_3)_2$ (10^{-2} M)	—	86	751
7	$C_{12}E_7$ + $Cu(NO_3)_2$ (10^{-2} M)	—	620	698
8	$Cu(DS)_2$ (5.10^{-3} M)[b]	6243	3161	6245

[a] Dodecyl heptaoxyethylene ether;
[b] Copper didodecyl sulfate

The micellar effect on the *endo/exo* diastereoselectivity of the reaction has also been investigated. The *endo/exo* ratio of the reaction of cyclopentadiene with methyl acrylate is affected little (compared to water) by the use of SDS and CTAB [73b], while a large enhancement was observed in SDS solution when *n*-butyl acrylate was the dienophile used [74]. The ratio of *endo/exo* products in the reaction of **1** with **113c** is not affected by CTAB, SDS and $C_{12}E_7$ [72a].

Recently Diego-Castro and Hailes [75] carried out a careful investigation on the effect of cationic surfactant CTAB and anionic surfactant SDS on the reactivity and stereoselectivity of aqueous Diels–Alder reaction between cyclopentadiene and a range of acrylate esters at room temperature. The surfactants were used at their critical micellar concentration, and the pH effect of the aqueous solution was also investigated to determine the optimum conditions for obtaining the highest diastereoselectivity. Some results are reported in Table 4.17, together with those obtained in the absence of surfactant, after reaction times of 4 h and 72 h. As the reaction time increases the *endo/exo* decreases because of the reversibility of Diels–Alder reactions that favor the more thermodynamically stable *exo* adduct. The *endo/exo* ratio decreases as the chain length of the acrylates increases. The pH of the aqueous medium also plays an

Table 4.17 CTAB effect on the Diels–Alder reactions between cyclopentadiene and acrylate esters



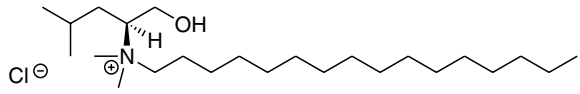
A (*endo*) **B** (*exo*)

	H_2O				H_2O+ CTAB			
	4 h		72 h		4 h		72 h	
R	Yield[a]	**A/B**	Yield[a]	**A/B**	Yield[a]	**A/B**	Yield[a]	**A/B**
Me	5	9.3	89	6.6	21	18	80	6.5
Et	65	6.0	79	4.8	92	7.2	92	5.5
$Me(CH_2)_8$	35	1.8	80	1.7	29	1.2	70	1.7

[a] Yield (%)

important role. Thus when the cycloaddition of nonyl acrylate with cyclopentadiene was carried out in water alone, the highest diastereoselectivity (*endo/exo* = 2.3) was observed at pH 3, while when the reaction was performed in the presence of CTAB at the same pH values a ratio of 1.7 was found and values higher than about 2.0 were not observed in the pH range 1 to 9.5.

The Diels–Alder reaction of nonyl acrylate with cyclopentadiene was used to investigate the effect of homochiral surfactant **114** (Figure 4.5) on the enantioselectivity of the reaction [77]. Performing the reaction at room temperature in aqueous medium at pH 3 and in the presence of lithium chloride, a 2.2:1 mixture of *endo/exo* adducts was obtained with 75% yield. Only 15% of *ee* was observed, which compares well with the results quoted for Diels–Alder reactions in cyclodextrins [65d]. Only the *endo* addition was enantioselective and the R enantiomer was prevalent. This is the first reported aqueous chiral micellar catalysis of a Diels–Alder reaction.



114

Figure 4.5

4.7 BIOCATALYST-PROMOTED DIELS–ALDER REACTION

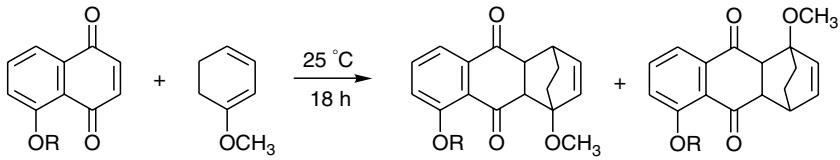
Biocatalysts have received great attention in these last few years. Due to their capacity to perform asymmetric transformations under mild conditions [78], they have been useful tools for synthesizing optically active organic molecules. They promote a variety of chemical transformations, including the syntheses of esters and amides and oxidations, reductions, eliminations and carbon–carbon forming. Little is known about biocatalyst-promoted Diels–Alder reactions.

4.7.1 Proteins and Enzymes Catalysis

The aqueous [4+2] cycloaddition reaction of 1,4-naphthoquinones **115** with methoxy cyclohexadiene performed in the presence of bovine serum albumin (BSA) is one of the first examples of protein-promoted Diels–Alder reactions [79]. Some results are reported in Table 4.18. The globular protein does not affect the regioisomer ratio of adducts. The highest enantiomeric excess was obtained in the cycloaddition of juglone **115** (R = H) with 1-methoxy-1,3-cyclohexadiene **116**.

Rao and colleagues [80] reported the first example of baker's yeast-catalyzed Diels–Alder reaction. Reactions of cyclopentadiene **(1)** with dienophiles **119** and **120** (Scheme 4.21) in the presence of baker's yeast at pH 7.2 afford prevalently the *exo* adduct with the exception of crotonic acid **120a**.

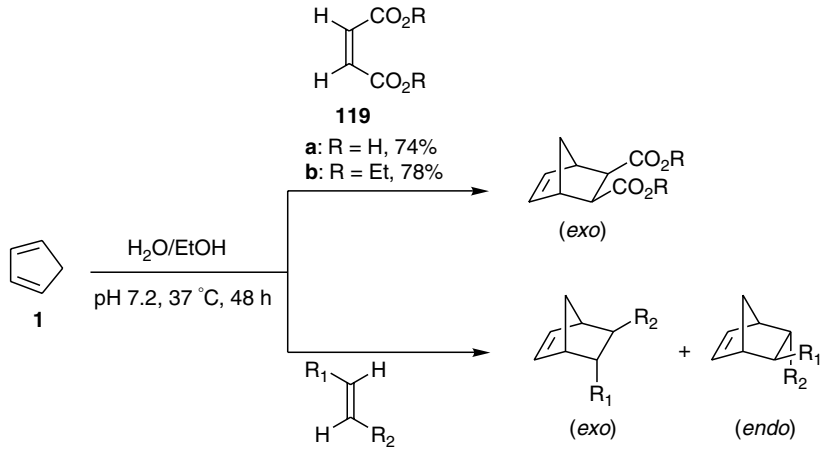
Table 4.18 Diels–Alder reactions in aqueous medium in the presence and in the absence of bovine serum albumin



115 **116** **117** **118**

R	Conditions	**117/118**	Yield (%)	ee (%)
H	H_2O	2.5:1	99	
H	H_2O/BSA	2.5:1	41[a]	38
Me	H_2O	1:7.5	99	
Me	H_2O/BSA	1:6	76	3
n-C_8H_{17}	H_2O	1:4	58	
n-C_8H_{17}	H_2O/BSA	1:3.5	67	0

[a] Dehydrogenated isomeric adducts were also present.



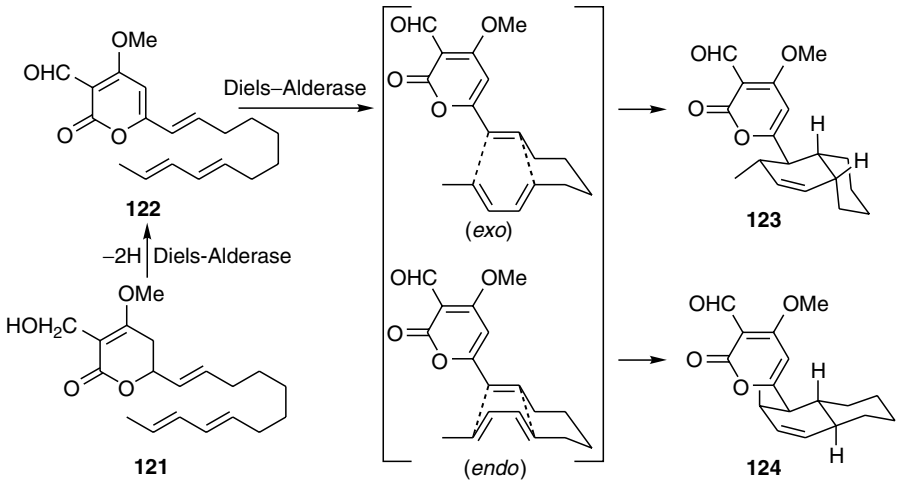
	endo/exo			
Medium, Cat.	**119a**	**119b**	**120a**	**120b**
H_2O	98:2	93:7	100:0[a]	100:0[a]
H_2O + baker's yeast	0:100	0:100	90:10	3:97

[a] reaction yield very low.

DropBooks

Scheme 4.21

The involvement of Diels–Alder reactions in the biosynthesis of naturally occurring compounds was hypothesized at least 20 years ago, but *Diels–Alderase*, the enzyme that catalyzes the reaction, was only isolated by Oikawa and colleagues [81] in 1995 in extracts of *Alternaria solani*, a fungus that causes early blight disease in potato and tomato plants. The fungus produces toxins known as solanapyrones which were biosynthesized via Diels–Alder reaction with *exo* selectivity, which cannot be achieved via usual chemical synthesis. Laboratory experiments show that the crude enzyme, containing solanapyrone synthase, catalyzes the Diels–Alder reaction of prosolanapyrone **122** to give the (–)-solanapyrone A **123** with excellent enantioselectivity (99 % *ee*) and relatively high *exo*-selectivity (6:1) (Scheme 4.22). Interestingly the solanapyrone synthase also catalyzes the oxidation of prosolanapyrone **121** to **122**, so a single enzyme catalyzes a two-step reaction of **121** to **123**. The biosynthesis of solanapyrones via Diels–Alder reaction has also been proposed [81b,c].



Substrate	Medium, cat.	T(°C)	t(h)	124/123	Yield (%)
122	H_2O	110	3	96:4	62
121	H_2O, pH 7 Enzyme	30	2	15:85[a]	61

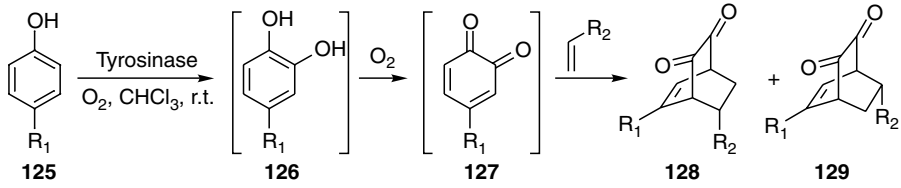
[a] **123** *ee* > 98%; **124** *ee* = 67%

Scheme 4.22

An interesting combination of enzymatic with non-enzymatic transformation in a one-pot three-step multiple sequence was reported by Waldmann and coworkers [82]. Phenols **125** in the presence of oxygen and enzyme tyrosinase are hydroxylated to catechols **126** which are then oxidized *in situ* to *ortho* quinones **127**. These intermediates subsequently undergo a Diels–Alder reaction with inverse electron demand by reaction with different dienophiles (Table 4.19) to give *endo* bicyclic 1,2-diketones **128** and **129** in good yields.

Another example of an enzymatic one-pot multiple Diels–Alder reaction is illustrated in Table 4.20 [83]. Racemic furfuryl alcohols **130** in the presence of ethoxy vinyl methyl fumarate **131** and enzyme TOYOBO-LIP undergo enzymatic acylation followed by kinetic enzymatic resolution to give the acyl derivatives **132** which then affords the adducts **133** and **134** by intramolecular Diels–Alder reaction; 3-methyl-furfuryl alcohol **130** (R = Me) in acetone gives the best results.

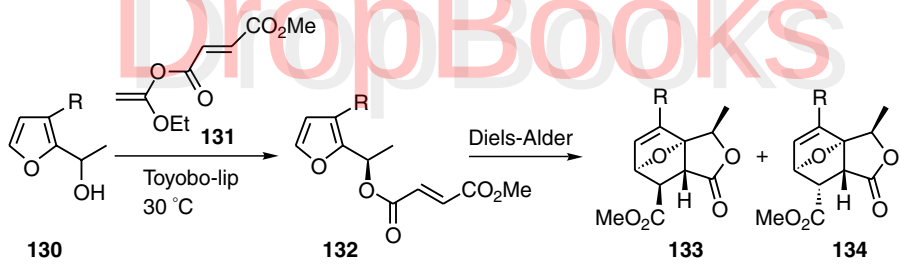
Table 4.19 Multiple hydroxylation–oxidation Diels–Alder reactions initiated by tyrosinase



125 **126** **127** **128** **129**

R_1	R_2	*t*(d)	**128/129**	Yield (%)
H	OEt	3	19	70
Me	OEt	2.5	33	77
i-Pr	OEt	2	1	70
Br	OEt	0.8	>99	43
F	OEt	0.8	>99	63
Me	OPr	1	3	85
Me	OBu	1	3	67
Me	OBu	1	3.2	78

Table 4.20 Asymmetric Diels–Alder reactions via enzymatic kinetic resolution



130 **132** **133** **134**

R	Solvent	*t*(d)	de	**133** (*ee*)	**134** (*ee*)	Yield (%)
H	Me_2CO	8	24	79	81	32
H	THF	8	24	81	48	28
Me	Me_2CO	1	100	84	—	43
Me	THF	1	100	84	—	37

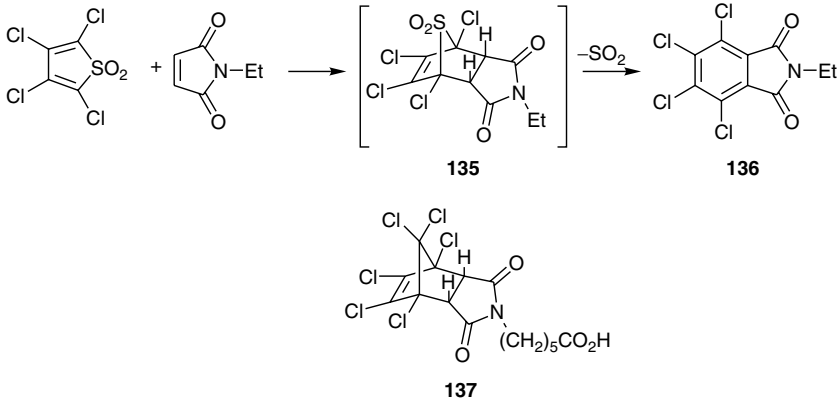
DropBooks

4.7.2 Antibody Catalysis

In the last 10 years organic chemists have shown great interest in antibodies that can promote a variety of chemical reactions, even those that are not catalyzed by natural enzymes [84].

The use of antibodies is based on the Jencks postulate which says that antibodies generated against an organic molecule resembling the transition state of a given reaction should catalyze this process [85]. Most monoclonal antibodies are prepared for synthetic purposes by displaying a small organic molecule (hapten), resembling the transition state of the reaction under study (generally reaction products or analogs), on a carrier protein to be recognized by the immune system that produces the antibody.

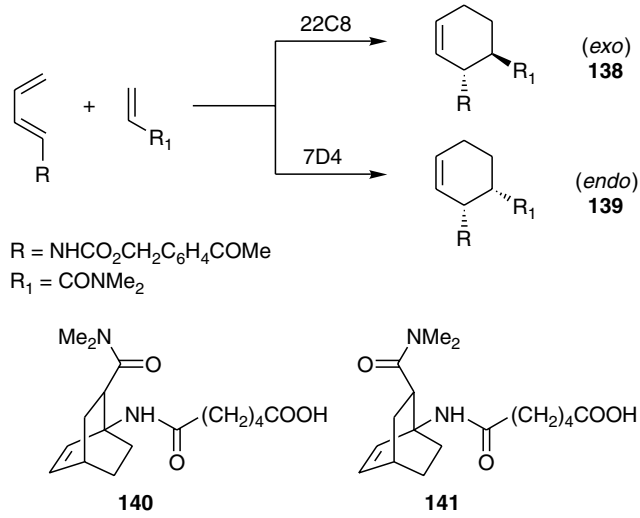
Catalytic antibody 1E9, the first catalytic antibody discovered for Diels–Alder reaction, catalyzes the cycloaddition between tetrachlorothiophene dioxide and N-ethylmaleimide (Equation 4.15) [86].



(4.15)

The reaction product **136** is not an appropriate hapten for generating catalytic antibody as it does not closely resemble the reaction intermediate **135**. Antibody 1E9 was prepared against hapten **137**, a stable analog of **135**, and the catalyst promoted the Diels–Alder reaction with multiple (> 50) turnovers.

Constrained bicyclo [2.2.2] octene haptens **140** and **141** elicit antibody catalysts 22C8 and 7D4 that change the stereoselectivity of the Diels–Alder reaction between 4-carbethoxy-*trans*-1,3-butadiene-1-carbamate and N,N-dimethylacylamide[87a] (Scheme 4.23). In the absence of catalysts, the *endo* adduct **139** is favored over the *exo* **138** both in refluxing toluene (66:34) and in aqueous buffer at 37 °C (85:15). Hapten **140** induces the antibody 22C8 which furnishes the *exo* adduct **138** exclusively with high enantioselectivity, while immunization with hapten **141**, that mimicked the *endo* approach, results in the antibody catalyst 7D4 that favors the formation of *endo* adduct **139**. A new approach to hapten design for elicitation of Diels–Alder catalytic antibodies by using the dicyclopentadienyl system of ferrocene as haptenic group has been successively developed [87b]. New *Diels–Alderases* have been produced that catalyze the cycloadditions depicted in Scheme 4.23 with high enantio- and diastereoselectivity [87b].



Scheme 4.23

4.8 BRØNSTED-ACID-CATALYZED DIELS–ALDER REACTION

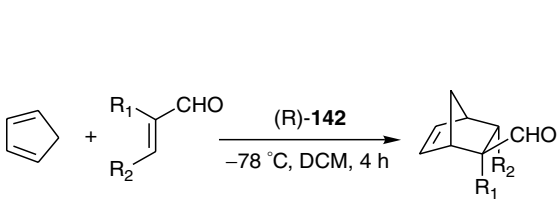
DropBooks

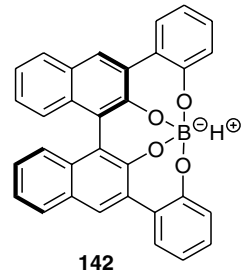
Brønsted-acid-catalyzed Diels–Alder reactions are not frequent because of the proton sensitivity of many dienes and cycloadducts, especially when long reaction times and high temperatures are required. Examples in aqueous medium involving imines activated by protonation as dienophiles and a proton-promoted Diels–Alder reaction of glyoxylic acid with cyclopentadiene are considered in Section 6.1.

The chiral catalyst **142** achieves selectivities through a double effect of intramolecular hydrogen binding interaction and attractive π–π donor–acceptor interactions in the transition state by a hydroxy aromatic group [88]. The exceptional results of some Diels–Alder reactions of cyclopentadiene with substituted acroleins catalyzed by (R)-**142** are reported in Table 4.21. High enantio- and *exo* selectivity were always obtained. The coordination of a proton to the 2-hydroxyphenyl group with an oxygen of the adjacent B–O bond in the nonhelical transition state should play an important role both in the *exo–endo* approach and in the *si–re* face differentiation of dienophile.

Trifluoromethanesulfonic acid (triflic acid) in toluene greatly activates the Diels–Alder reaction of benzaldehydes with dimethylated 1,3-butadienes [89] (Table 4.22). With mono-methylated 1,3-butadienes the reaction gives less

Table 4.21 Asymmetric Diels–Alder reactions catalyzed by (R)-**142**



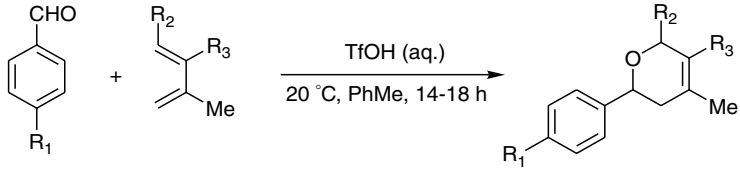


142

R_1	R	*ee* (%)	Yield (%)	*exo/endo*
Br	H	99	99	99:1
Me	H	99	99	99:1
Et	H	92	99	97:3
Me	Me	98	99	99:1

satisfactory yields and the Prins product in moderate yield and low diastereoselectivity was isolated. It is hypothesized that both reactions (*hetero*-Diels–Alder and Prins) occur via a common carbocation intermediate which can assume differently stabilized *cis* and *trans* forms depending on the presence or absence of the methyl group at C-2 in the butadiene moiety, which favor the formation of the Diels–Alder or the Prins adduct.

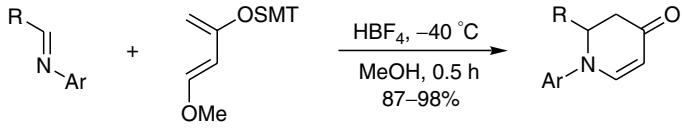
Table 4.22 Diels–Alder reactions catalyzed by triflic acid



	R_1	R_2	R_3	Yield (%)
	H	H	H	72
	H	H	Me	85
	H	Me	H	82[a]
	Cl	H	H	68
	NO_2	H	H	40
	OMe	H	H	14

[a] 1:1 mixture of diasteroisomers.

The fluoboric acid-catalyzed aza-Diels–Alder reaction of aldimine and Danishefsky's diene proceeds smoothly to afford dihydro-4-pyridones in high yields [90] (Equation 4.16). Unstable aldimines generated from aliphatic aldehydes can be prepared *in situ* and allowed to react under one-pot reaction conditions. This one-pot Brønsted acid-catalyzed three-component aza-Diels–Alder reaction affords the adducts in good to high yields.



(4.16)

Ar = Ph, *p*MeO-C_6H_4; R = Ph, PhCH=CH, *p*X-C_6H_4 (X = NO_2, Me)

Fluoboric acid is also an efficacious promoter of cyclic oxo-carbenium ions (Scheme 4.24) bearing an activated double bond which, in the presence of open-chain and cyclic dienes, rapidly undergo a Diels–Alder reaction [91]. Chiral α,β-unsaturated ketones bearing α'-hydroxy substituents, protected as acetals, react with various dienes in the presence of HBF_4, affording Diels–Alder adducts that were isolated as alcohols by hydrolysis of the acetal group by TsOH. Some examples of reactions with isoprene are reported in Table 4.23. The enantioselectivity of the reaction is dependent on the size of the substituent R on the α'-carbon: high levels of asymmetric induction were observed with R = *i*-Pr (90:1) and R = *t*-Bu (150:1) and low levels with R = Me (2.7:1) and R = Ph (3.0:1). Scheme 4.24 shows the postulated reaction mechanism.

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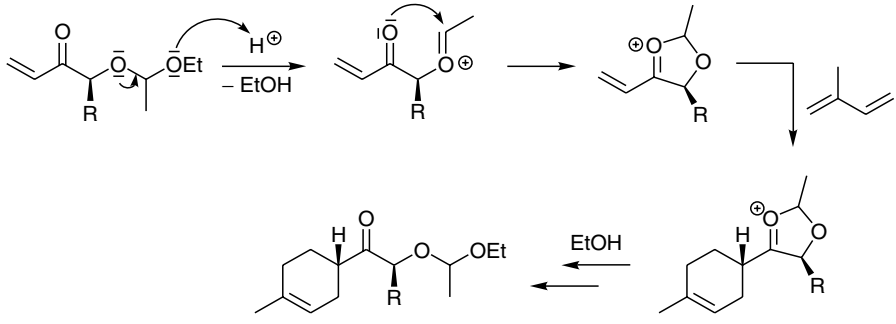
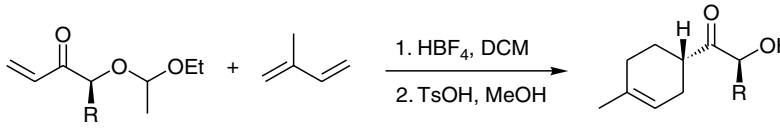
Gassman [92] has been a pioneer of ionic Diels–Alder reactions that proceed via *in situ* generation of cationic species (allylic cations) from olefinic precursors



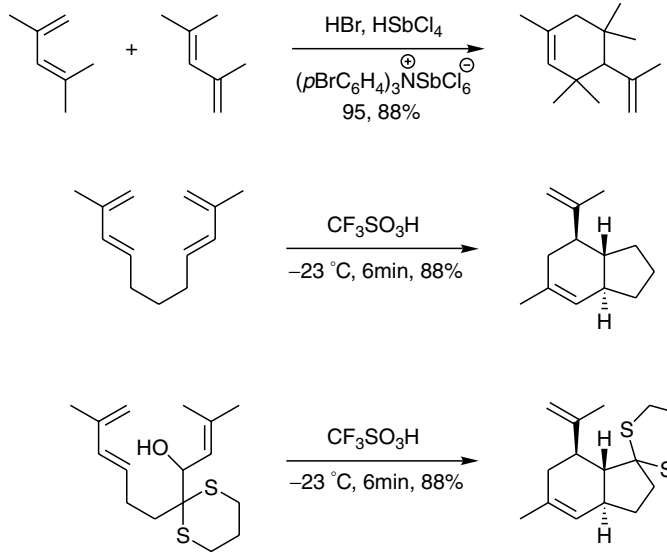
Scheme 4.24

Table 4.23 Diels–Alder reactions via vinyloxocarbenium ions



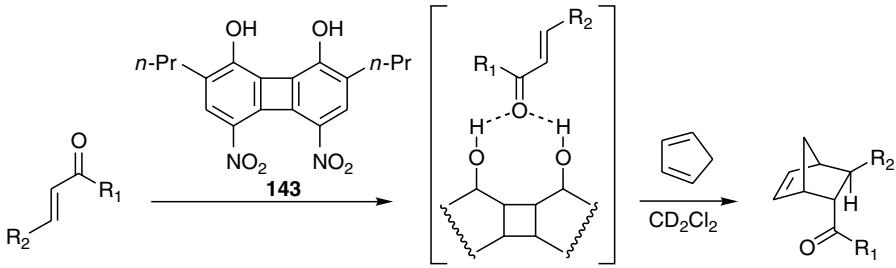
R	T (°C)	t (h)	Yield (%)
Me	−78	2	58
i-Pr	−45	10	70
t-Bu	−20	16	60
Ph	−20	16	70

by Brønsted acids. Some of these procedures that use protic acids and aminium cation radicals as catalysts are illustrated in Scheme 4.25. A stepwise mechanism has been proposed [92d].



Scheme 4.25

An alternative strategy for promoting Diels–Alder reaction by proton involves the activation of dienophile by hydrogen bonding [93]. Biphenylene diol **143** (Scheme 4.26) forms doubly hydrogen-bonded complexes with α,β-unsaturated carbonyl compounds, which strongly accelerate the Diels–Alder



				Yield (%)	
R_1	R_2	T (°C)	t (h)	with **143**	without **143**
Me	H	r.t.	0.16	90	3
H	H	r.t.	0.5	76	10
H	Me	55	45	95	21
H	Ph	55	73	74	13
Me	Me	55	3	83	25
OMe	Ph	55	144	13	13

Scheme 4.26

reactions. An ester group of acrylates blocks the formation of hydrogen bonds and consequently no acceleration is observed.

Examples of hydrogen-bonding-promoted Diels–Alder reactions obtained by using alcoholic and phenolic solvents are illustrated in Section 6.2.4.

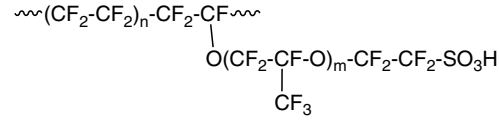
Nafion-H (**144**), a perfluorinated resin-sulfonic acid, is an efficient Brønsted-acid catalyst which has two advantages: it requires only catalytic amounts since it forms reversible complexes, and it avoids the destruction and separation of the catalyst upon completion of the reaction [94]. Thus in the presence of Nafion-H, 1,4-benzoquinone and isoprene give the Diels–Alder adduct in 80% yield at 25 °C, and 1,3-cyclohexadiene reacts with acrolein at 25 °C affording 88% of cycloadduct after 40 h, while the uncatalyzed reactions give very low yields after boiling for 1 h or at 100 °C for 3.5 h respectively [95]. Other examples are given in Table 4.24. In the acid-catalyzed reactions that use highly reactive dienes such as isoprene and 2,3-dimethylbutadiene, polymerization of alkenes usually occurs; with Nafion-H, no polymerization was observed.

Recently Nafion-H was successfully used in the Diels–Alder reaction of olefin acetals with isoprene and cyclopentadiene (Scheme 4.27). The reactions work well in DCM at room temperature and Nafion-H did not cleave the acetal group [96]. The recovered Nafion-H was used four or five times without affecting the yield of the cycloadducts.

DropBooks

Table 4.24 Nafion-H catalyzed Diels–Alder reactions in refluxing benzene

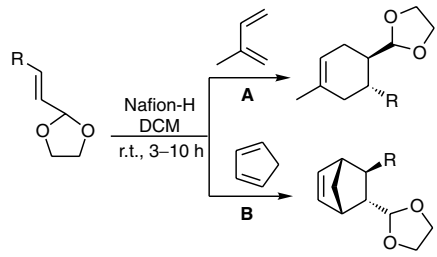
Reagents	*t* (h)	Yield (%)
MA + AN	5	87
BQ + AN	2	92
DMM + AN	15	95
DMF + AN	16	94
BQ + IS[a]	25	80
NQ + 2,3-DB	36	93
AC + 1,3-CH[a]	40	88



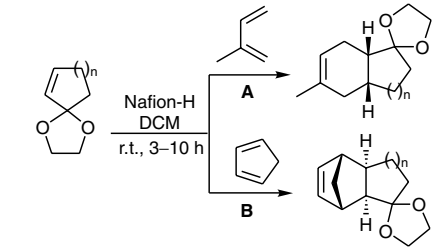
Nafion-H (**144**)

[a] At 25 °C in CCl_4.

MA = maleic anhydride; BQ = *p*-benzoquinone; DMM = dimethylmaleate; DMF = dimethyl fumarate; NQ = naphthoquinone; AC = acrolein; AN = anthracene; IS = isoprene; 2,3-DB = 2,3-dimethylbutadiene; 1,3-CH = 1,3-cyclohexadiene.



R	Reaction	*t* (h)	*endo/exo*	Yield (%)
Me	**A**	7		80
Me	**B**	10	85:15	81
Ph	**A**	8		79
Ph	**B**	12	90:10	84



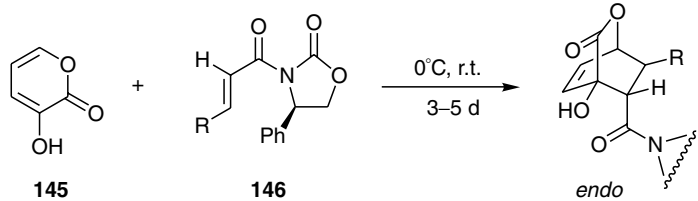
n	Reaction	*t* (h)	*endo/exo*	Yield (%)
1	**A**	4		68
1	**B**	4	96:4	68
2	**A**	3		92
2	**B**	4	95:5	89
3	**A**	4		94
3	**B**	4	80:20	91

Scheme 4.27

4.9 MISCELLANEOUS DIELS–ALDER REACTIONS

Base-catalyzed Diels–Alder reactions are rare (Section 1.4). A recent example is the reaction of 3-hydroxy-2-pyrone (**145**) with chiral N-acryloyl oxazolidones **146** that uses cinchona alkaloid as an optically active base catalyst [97] (Table 4.25). Only *endo* adducts were obtained with the more reactive dienophile **146** (R = H), the best diastereoselectivity and yields being obtained with an *i*-PrOH/H_2O ratio of 95:5. The reaction of **146** (R = Me) is very slow, and a good adduct yield was only obtained when the reaction was carried out in bulky alcohols such as *t*-amyl alcohol and *t*-butanol.

Table 4.25 Diels–Alder reactions of 3-hydroxy-2-pyrone (**145**) catalyzed by cinchona alkaloids



145 **146** *endo*

R	Base	Solvent	de (%)[a]	Yield (%)
H	Et_3N	*i*-PrOH-H_2O[b]	82	99
H	CID[c]	*i*-PrOH-H_2O	95	93
H	CIN[d]	*i*-PrOH-H_2O	79	97
H	QUN[e]	*i*-PrOH-H_2O	94	100
H	QUD[f]	*i*-PrOH-H_2O	84	97
Me	Et_3N	DCM	59	65
Me	CID[c]	$EtMe_2COH$	72	96
Me	CID[c]	*t*-BuOH	81	87

[a] de (%) of *endo* adduct;
[b] 95:5;
[c] Cinchonidine;
[d] Cinchonine;
[e] Quinine;
[f] Quinidine

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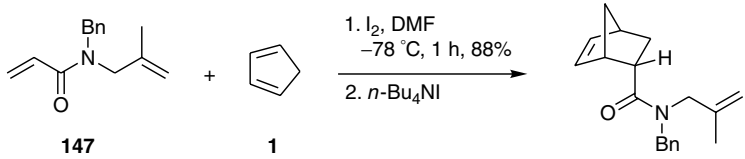
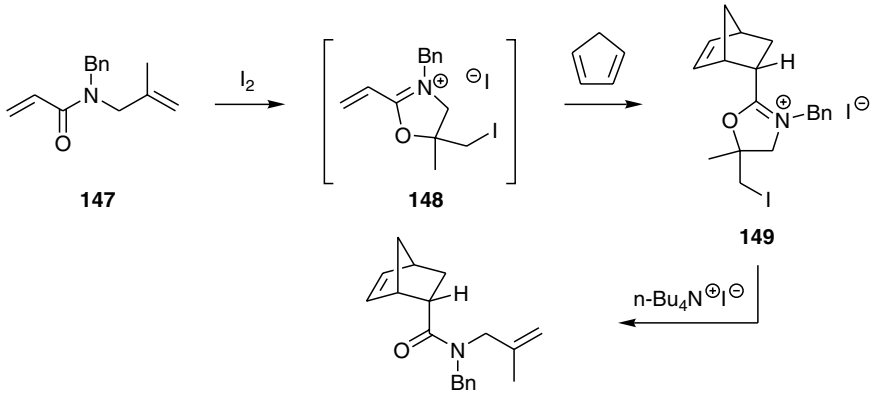
Diels–Alder reaction of dienophiles, N-allylic enamides and α,β-unsaturated lactam derivatives with open chain and inner ring dienes is promoted by iodine [98]. Thus the cycloaddition of N-benzyl-N-methallyl acrylamide **147** with cyclopentadiene (**1**) proceeds smoothly in DMF at −78 °C in the presence of I_2 (2 eq.) to give a prevalence of *endo* adduct (75 %) in 88 % yield (Equation 4.17).

In contrast, the reaction of **147** with **1**, in the absence of catalyst, affords traces of adduct after 3 days. The activation by I_2 is due to the formation of cationic iodolactonization intermediate **148** (Scheme 4.28) which reacts easily with the diene, affording the dihydrooxazole **149** which is then treated with $Bu_4N^{\oplus}I^{\ominus}$ to give the final adduct. With some substrates, this method of activation was proved to be more effective than the use of Lewis acids.

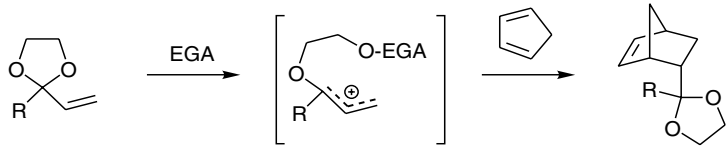


147 **1** *endo/exo* = 3:1 (4.17)



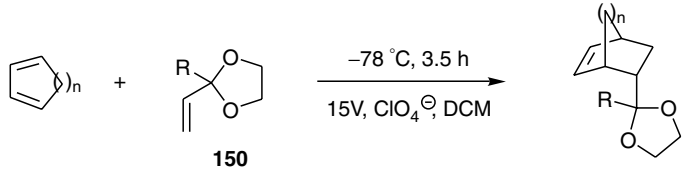
Scheme 4.28

Electrochemical ionic Diels–Alder reaction has been successfully used to promote the reaction of ethylene acetals **150** with several carbo-dienes [99]. Some examples are presented in Table 4.26. These Diels–Alder reactions catalyzed by electrogenerated acid (EGA) were carried out by using platinum electrodes in DCM containing $LiClO_4$ and Bu_4NClO_4 as a source of acid catalyst. Higher *endo* selectivities than that obtained in the thermal reactions were observed. Reasonably, the reaction proceeds through a highly reactive allyl cation generated by the action of EGA (Equation 4.18).



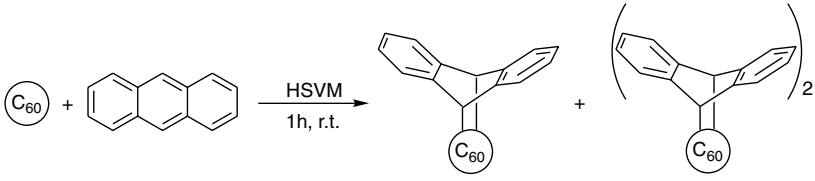
(4.18)

Table 4.26 Electrochemical ionic Diels–Alder reactions



n	R	*endo/exo*	Yield (%)
1	H	4.8	84
1	Me	50	85
1	Et	8.2	82
2	Me	9.8	85
2	Et	7.9	76

The *high-speed vibration milling* (HSVM) technique was recently applied to the Diels–Alder reaction of fullerene C_{60} with condensed aromatics such as anthracene, tetracene, pentacene and naphtho[2,3-a]pyrene [100]. This is a type of mechanochemical reaction in which the mechanical energy is used as a driving force of the reaction. Thus fullerene C_{60} and anthracene, vigorously shaken in a stainless steel capsule with a milling ball at a rate of 3500 cycles per minute for 1 h, afford monoadduct **151** and bisadduct **152** in 55% and 19% yield, respectively, with 12% unchanged C_{60} (Equation 4.19). The monocycloadduct was isolated in better yield than in the reaction in solution. Good yields of monoadducts were also obtained for the other condensed aromatics. The HSVM methodology is particularly advantageous for reactions which involve reactants that are hardly soluble in organic solvents.



151 **152** (4.19)

Among special chemical methods that facilitate the Diels–Alder reaction can be included the *temporary metal connection* strategy [101] that is illustrated in Table 4.27. Si, Mg and Al are used as temporary connectors of diene and dienophile moieties. The cycloaddition occurs easily due to its intramolecular nature and because the dienophilic component of reagent is now formally a vinyl carbon ion (i.e. a vinyl carbanion in **154** with $M = AlEt_2^{\ominus}$). Thus the metal-tethered **154**, prepared from lithium alkoxide of **153** with the suitable metal vinyl halide, gives, by heating, the cycloadducts **156** and **157**, through the

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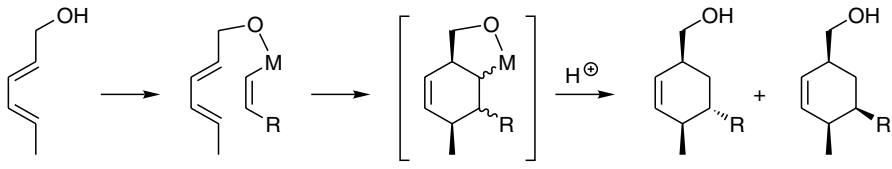
Table 4.27 Diels–Alder reactions by temporary metal connection



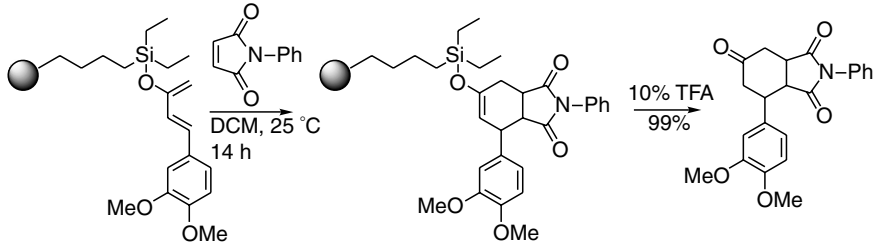
153 **154** **155** **156** **157**

M	R	*T* (°C)	*t* (h)	**156**/**157**	Yield (%)
Mg	H	80	1	100:0	70
$SiMe_2$	H	160	3	100:0	70
$AlEt_2^{\ominus}$	H	130	3	100:0	75
Mg	Me	130	2	9:1	60
$AlEt_2^{\ominus}$	Me	150	6	5.6:1	70

intermediates **155**, that were isolated in good yield after acidification with hydrochloric acid.

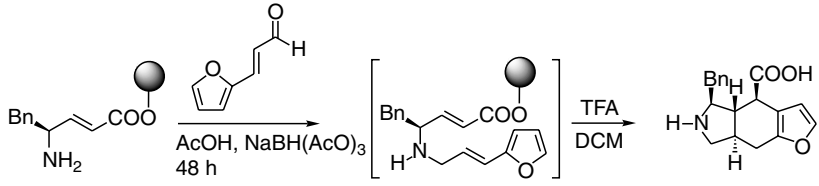
4.10 OUTLINED DIELS–ALDER REACTIONS

A polymer-supported silyl triflate and subsequent functionalization: synthesis and solid-phase Diels–Alder reactions of silyloxydienes [25]



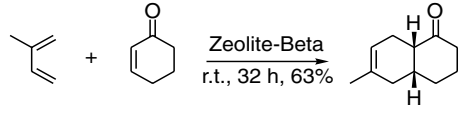
13 examples

Solid-phase Diels–Alder reactions of amino acid derived trienes [23]



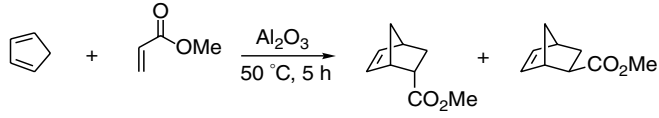
7 examples

Zeolite and Lewis-acid catalysis in Diels–Alder reactions of isoprene [20b]



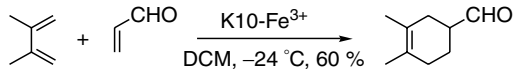
various zeolites

The cycloaddition reactions of unsaturated esters with cyclopentadiene on γ-alumina [18]

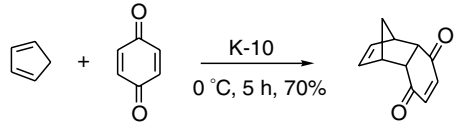


endo/exo ratio and yield depend on alumina activity

Acceleration of the Diels–Alder reaction by clays suspended in organic solvents [7]

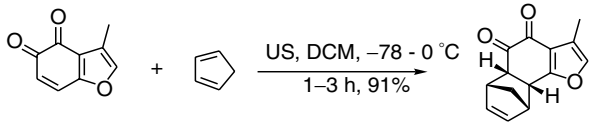


Cycloadditions with clays and alumina without solvent [8]



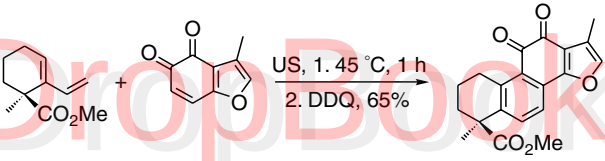
23 examples

Ultrasound-promoted cycloadditions in the synthesis of *Salvia miltiorrhiza* [30b]



9 examples

Asymmetric synthesis of *Salvia miltiorrhiza* abietanoid *o*-quinones: methyl tanshinonate, tanshinone IIB, tanshindiol B and 3-hydroxytanshinone [30c]



(–)-(S) (–)-(S)

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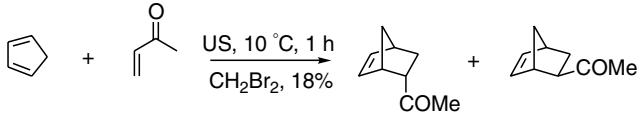
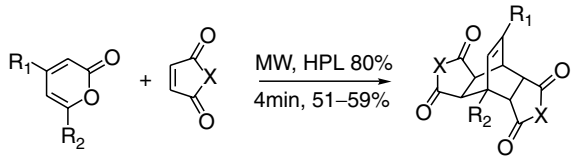
On sonochemical effect on the Diels–Alder reaction [33]



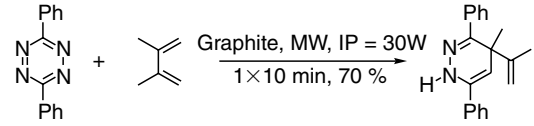
95.1% 4.9%

The Diels–Alder reaction of 2H-pyran-2-ones: part IV – Microwave catalyzed Diels–Alder reaction of 4,6-disubstituted-2H-pyran-2-ones with 1,4-naphthoquinone and N-phenylmaleimide [41a]



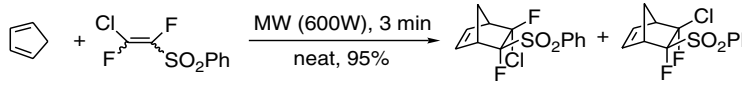
X = O, NPh R_1 = pMeO-C_6H_4 R_2 = pMeO-C_6H_4, Me

Microwave-assisted Diels–Alder reactions supported on graphite [39a]



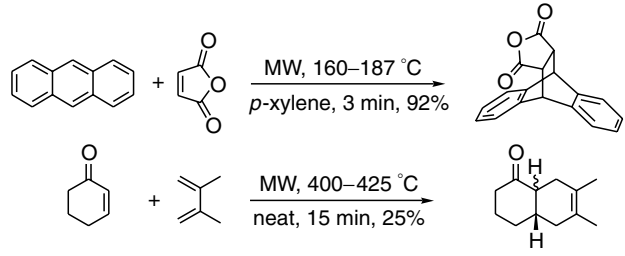
5 examples

Microwave-activated Diels–Alder cycloaddition reactions of 1,2-difluoro-1-chlorovinyl-phenylsulfone [102]

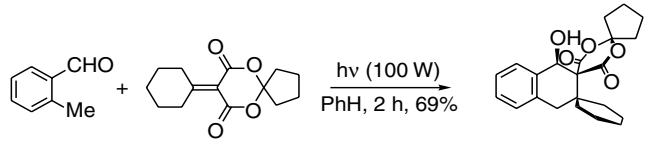


dienes: furan, 1,3-diphenylisobenzofuran

Application of commercial microwave ovens to organic synthesis [103]

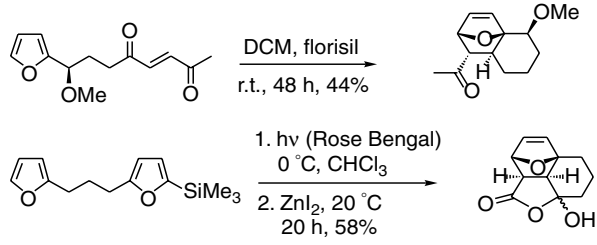


Diels–Alder reactions of photoenol of 2-methylbenzaldehyde with 5-alkylidene-1,3-dioxane-4,6-dione derivatives [48]

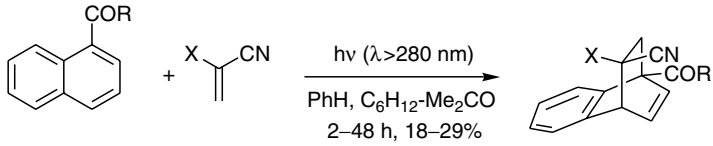


11 examples

Stereoselectively synthesis of decalines via tandem photooxidation-intramolecular Diels–Alder reactions of bis-furan [104]

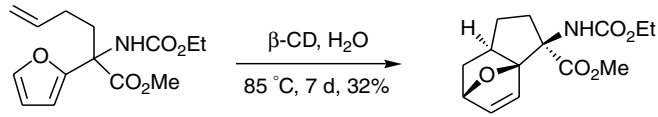


1,4-Photoaddition of -morpholinoacrylonitrile to 1-acylnaphthalenes [105]



R = H, Me, Ph X = Morpholino, S-*t*-Bu

Intramolecular Diels–Alder reactions of the furan diene (IMDAF); rapid construction of highly functionalized isoquinoline skeletons [65i]



3 examples

The kinetic effects of water and of cyclodextrins on Diels–Alder reactions. Host–guest chemistry, part 18 [65c]

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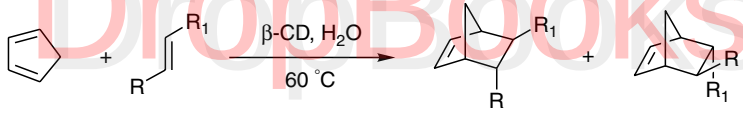
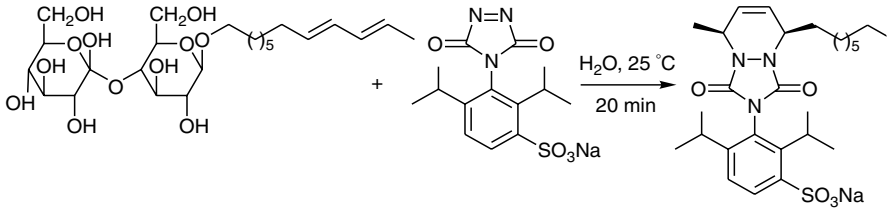


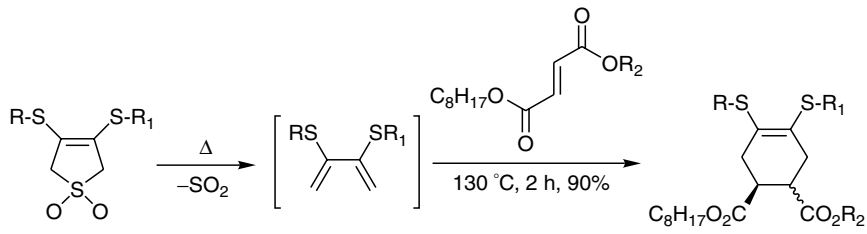
R = CN, CO_2Et, CO_2Bu, CO_2Pr, COMe, CO_2H, $CO_2C_6H_{11}$

R_1 = H, CO_2Et, CO_2H, Various solvents

Detergents containing a 1,3-diene group in the hydrophobic segment. Facile chemical modification by a Diels–Alder reaction with hydrophilic dienophiles in aqueous solution [69]

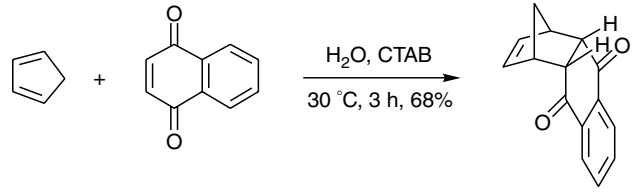


Regioselectivity of Diels–Alder reactions of surfactant 1,3-diene with surfactant dienophiles [70b]

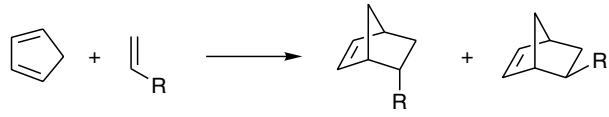


R = pC_8H_{17}-C_6H_4 R_1 = $(CH_2)_4NMe_3Br$ R_2 = $(CH_2)_6NMe_3Br$

Micellar catalysis $\pi^{4s} + \pi^{2s}$ cycloaddition in aqueous media [72b]

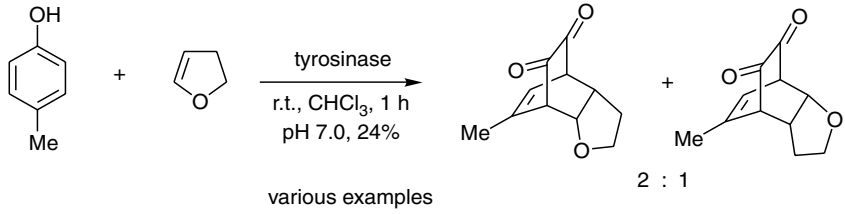


(4 + 2) Cycloadditions in micelles: a comparison of the product spectrum and reaction rate with reactions in solution [74]

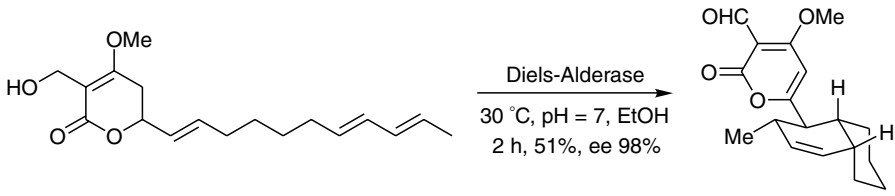


R = CN, CO_2Me, CO_2Bu various surfactants; various solvents

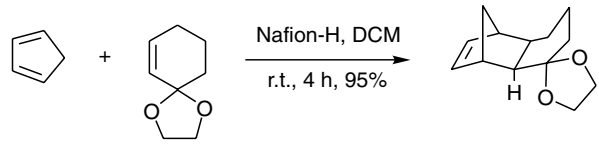
An enzyme-initiated hydroxylation–oxidation carbo-Diels–Alder domino reaction [82]



Total synthesis of (−)-solanapyrone A via enzymatic Diels–Alder reaction of prosolanapyrone [81b]



Studies in Lewis acid and $LiClO_4$ (or nafion-H) catalyzed ionic Diels–Alder reactions of chiral and achiral olefinic acetals respectively [96]



6 examples

endo/exo = 95:5

Diastereoselective Diels–Alder reactions via cyclic vinyloxocarbenium ions [91]

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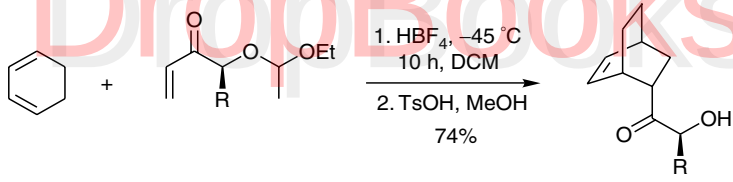
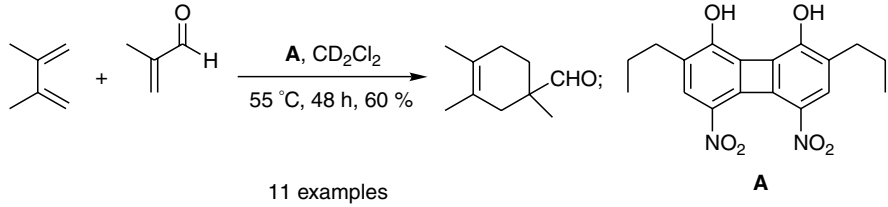


6 examples

de = 75:1

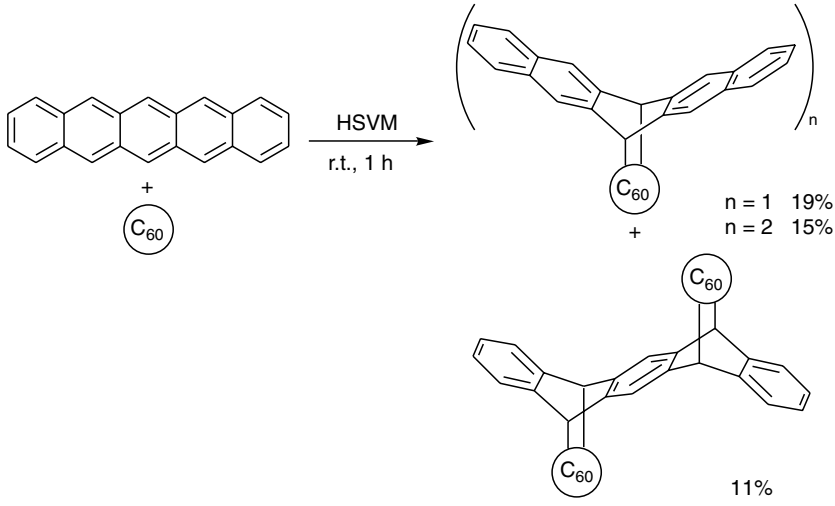
Diels–Alder reactions: rate acceleration promoted by a bisphenylendiol [93c]



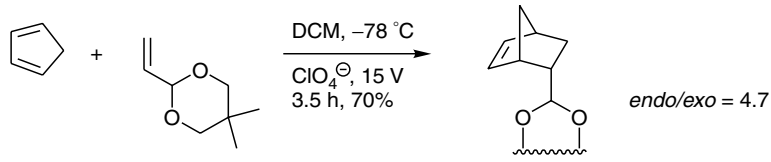
11 examples

A

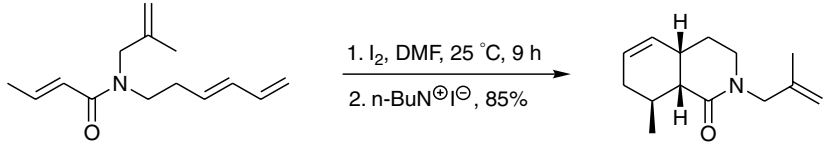
Solid-state [4 + 2] cycloaddition of fullerene C60 with condensed aromatics using a high-speed vibration milling technique [100]



An *endo*-selective ionic Diels–Alder reaction of α,β-enone and α,β-enal acetals catalyzed by electrogenerated acid [99]



Diels–Alder reaction of N-allylic enamides and lactam derivatives through iodine-mediated activation [98]



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5 High Pressure Diels–Alder Reaction

5.1 INTRODUCTION

Although the Diels–Alder reaction provides a rapid and convergent entry to complex polycyclic molecules, its application may sometimes be unsuccessful due to the low reactivity of reagents, diene and dienophile, and/or instability of both reagents and cycloadducts under thermal or Lewis-acid-catalyzed conditions [1]. In these cases considerable improvements have been made by applying high pressure [2]. The use of this technique is now common in the laboratory as well as in industry, since even modest pressures may have marked effects on reactions in solution. A significant example is the cycloaddition reactions of 3-methyl-2-cyclopenten-1-one **(1)** and 3-methyl-2-cyclohexen-1-one **(2)** with open chain dienes [3] **3** (Equation 5.1). These β-substituted cycloalkenones are known to be unreactive dienophiles due to the steric and electronic effects of the methyl group at the ethylenic β-carbon [4]. Thermal and catalyzed cycloadditions do not occur at atmospheric pressure, thus precluding the ready preparation of *cis*- and *trans* angularly methylated hydrindanones **4** and **6** and octalones **5** and **7**, in which the angular methyl group is in a 1,3-positional relationship with the keto function. The application of high pressure (12–15 kbar) in combination with a Lewis-acid catalyst, $EtAlCl_2$, accelerated the reactions, offering a straightforward route [3] to these methylated bicyclic compounds which are useful intermediates in the synthesis of natural products.

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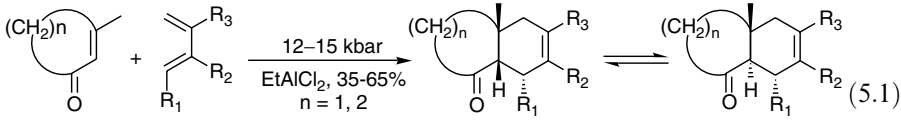


(5.1)

1 **3** **4** **6**
2 R_1, R_2, R_3= H, Me **5** **7**

The term 'high pressure' means in the range 1–20 kbar (0.1–2 GPa). These pressures can be obtained with a relatively simple piston-cylinder apparatus. The Diels–Alder reaction exhibits a large negative activation volume, $\Delta V^{\ddagger}$ which is the only transition state property that can readily be determined in absolute terms [5]. Diels–Alder cycloaddition also exhibits a large negative molar reaction volume, ΔV. Intermolecular cycloadditions have larger negative volumes (about -25 to $-45\,cm^3\,mol^{-1}$) than the intramolecular ones.

High pressure can influence reactions characterized by negative molar and activation volumes in the following aspects: (i) acceleration of the reaction, (ii) modification of regioselectivity and diastereoselectivity, and (iii) changes in chemical equilibria. The pressure dependence on the rate constant of the reaction is expressed as follows:

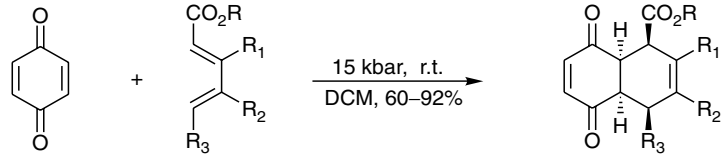
$$\frac{\delta \ln k}{\delta P} = -\frac{\Delta V^{\ddagger}}{RT}$$

If $\Delta V^{\ddagger}$ is negative, the rate constant will increase with increasing pressure. Similarly, the effect of pressure on the reaction equilibria is given by the following equation:

$$\frac{\delta \ln K}{\delta P} = -\frac{\Delta V}{RT}$$

If ΔV is negative, the application of pressure shifts the equilibrium toward the products.

An interesting example of accelerating a reaction when high pressure is applied is the synthesis of a series of highly functionalized 4a,5,8,8a-tetrahydro-1,4-naphthalenediones **10** by cycloaddition of *p*-benzoquinone **(8)** with a variety of electron-poor dienic esters **9** at room temperature (Equation 5.2) reported by Dauben and Baker [6]. Using conventional methods, these heat-sensitive cycloadducts are difficult to synthesize free of the isomeric hydroquinones. When the reactions were carried out under thermal conditions, the primary cycloadducts were mostly converted into the corresponding hydroquinones.

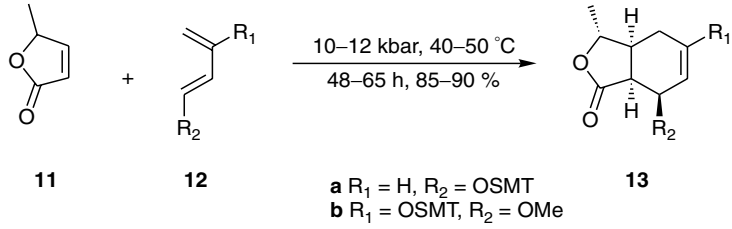


(5.2)

8 **9** **10**

R, R_1, R_2, R_3 = H, Me, Et, $CH_2OSMDBT$

The cycloaddition of the poor reactive dienophile *β*-angelica lactone **(11)** with open chain dienes **12** is another interesting example of activation by high pressure [7]. Since high temperatures and/or the catalysis of strong Lewis acids are precluded due to the diene sensitivity, the cycloaddition reactions cannot be carried out at atmospheric pressure. The resulting cycloadducts **13** are of interest because they are versatile synthetic building blocks. High pressure allowed the reactions to occur under milder conditions in high yields (85–90 %) (Equation 5.3).



11 **12** **13**

a R_1 = H, R_2 = OSMT
b R_1 = OSMT, R_2 = OMe

(5.3)

Pressure also provides a valuable tool in the control of the regio-and diastereoselectivity of the Diels–Alder cycloaddition. This effect is influenced by the difference between the activation volumes of parallel reactions leading to regio- and diastereoisomers. A higher *endo*-diastereoselectivity can generally be expected because the *endo* transition state has a larger negative activation volume than the *exo* transition state. An example of regio- and stereocontrol by high pressure is the cycloaddition of the cyclohexenone-like dienophile **14** with diene **15** [7, 8] that affords the tetracyclic compound **16** which is used for the synthesis of aklavinone **17** (Scheme 5.1), the aglicone component of several members of 11-deoxyanthracyclines.

Until the 1980s this technique was used mostly in mechanistic investigations to obtain information about the structure and properties of the transition state of the Diels–Alder reaction. Now, the technique is mainly used in applications of synthetic organic chemistry.

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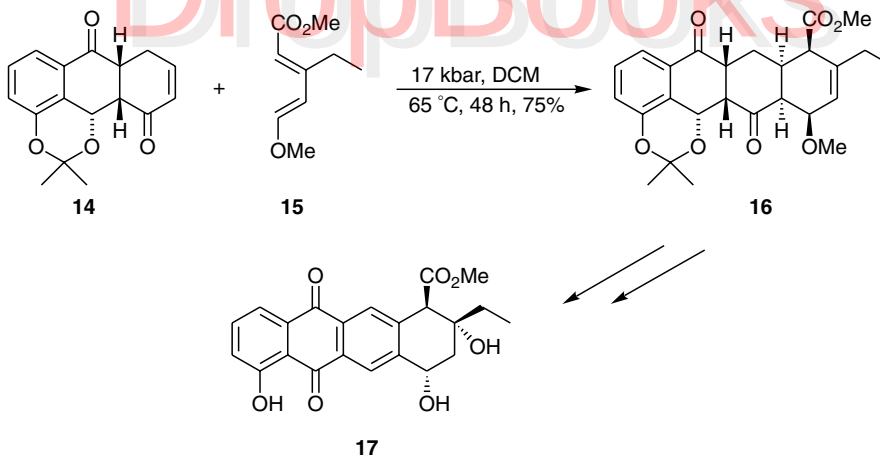


14 **15** **16** **17**

Scheme 5.1

The solvent may be an important parameter for reactions carried out in solution, since the value of activation volume is often dependent on the solvent. A limitation may be due to the effect of pressure on the freezing temperature of

the solvent. To prevent the solvent from freezing under high pressure, temperature elevation is mostly used.

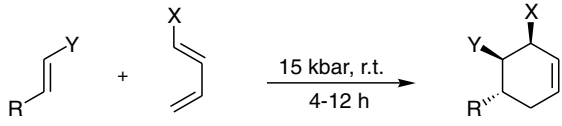
5.2 OPEN-CHAIN DIENES

5.2.1 Cycloadditions with Carbodienophiles

Cycloaddition reactions of (E)-1-acetoxybutadiene **(18a)** and (E)-1-methoxybutadiene **(18b)** with the acrylic and crotonic dienophiles **19** were studied under high pressure conditions [9] (Table 5.1). Whereas the reactions of **18a** with acrylic dienophiles regioselectively and stereoselectively afforded only *ortho-endo*-adducts **20** in fair to good yields, those with crotonic dienophiles did not work. Similar results were obtained in the reactions with diene **18b**. The loss of reactivity of the crotonic dienophiles has been ascribed to the combination of steric and electronic effects due to the methyl group at the β-carbon of the olefinic double bond.

The study was extended to the inverse electron-demand Diels–Alder reaction between the (E)-1-carboalkoxybutadienes **21** with ethylvinylether **22** (Figure 5.1). No reaction was observed in any case; either the starting materials were recovered or polymeric material was produced.

Table 5.1 High pressure Diels–Alder reactions of (E)-1-acetoxy- (**18a**) and (E)-1-methoxybutadiene (**18b**) with acrylic and crotonic dienophiles



19 **18 a**, X = OAc **b**, X = OMe **20**

X	Y	R	Yield (%)
OAc	CHO	H	81
OAc	CHO	Me	5
OAc	COMe	H	45
OAc	COMe	Me	0
OAc	CO_2Me	H	19
OAc	CO_2Me	Me	0
OAc	CN	H	5
OAc	CN	Me	0
OMe	CHO	H	47
OMe	CHO	Me	30
OMe	CO_2Me	Me	0

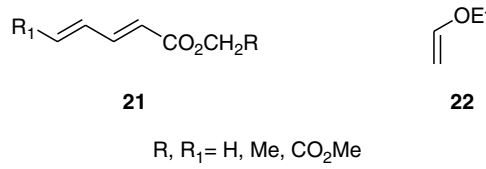
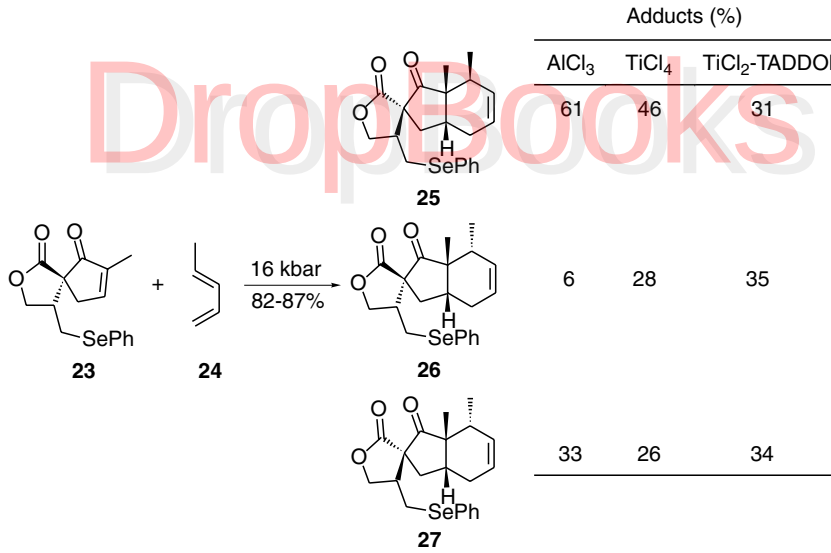


Figure 5.1

The Diels–Alder reaction of the bicyclospirolactone **23** with E-piperylene **(24)** is the key step in a stereocontrolled synthetic approach to tricyclic compounds **25–27** related to Bakkenolides [10]. The cycloaddition failed at ambient pressure, but proceeded in generally good yield at high pressure and in the presence of various Lewis acids, giving mixtures of the *anti-endo* **25** (with respect to the CH_2SePh group), *syn-endo* **26** and *anti-endo* **27** cycloadducts (Scheme 5.2). The cycloadditions were totally regioselective and the facial diastereoselectivity seems to be dependent upon the nature of the catalyst. The preponderance of *endo* products was attributed to high pressure.



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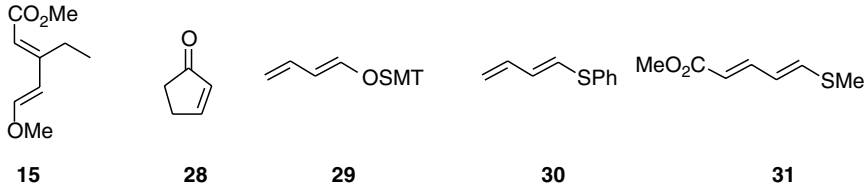
Scheme 5.2

α,β-Unsaturated cycloalkenones are very poorly reactive dienophiles [11] that require high temperatures to afford cycloadducts in good yields. These conditions, as well as the use of strong Lewis acids as catalysts, are precluded if sensitive *hetero*-substituted 1,3-butadienes are used. Cycloalkenone cycloadditions

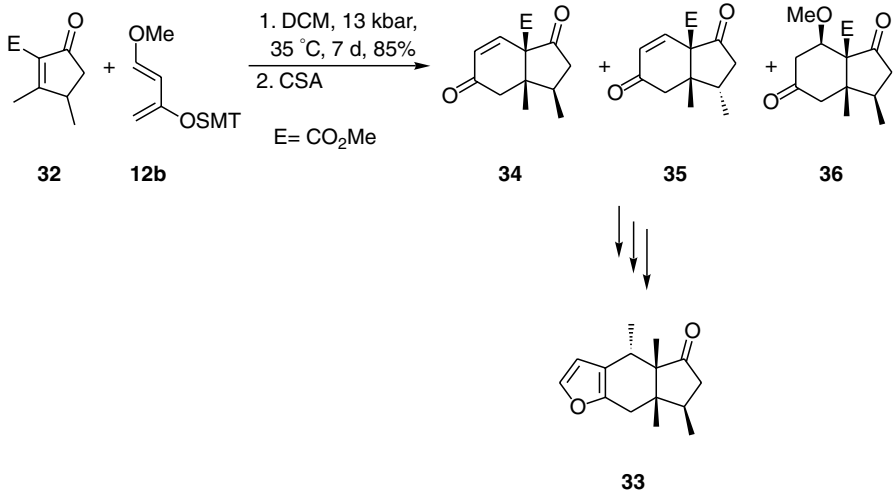
may, however, be accelerated by pressure, thus occurring under milder conditions which often improve also selectivity. 2-Cyclopenten-1-one **(28)** reacts regioselectively and stereoselectively [7, 12] with the electron-rich and push–pull *hetero*-substituted butadienes **15** and **29** in good to high yield (Figure 5.2). The replacement of oxygen by sulfur resulted in a markedly decreased diene reactivity as shown by the complete failure of **30** and **31** (Figure 5.2) to react.



15 **28** **29** **30** **31**

Figure 5.2

High pressure Diels–Alder reaction of 1-methoxy-3-(trimethylsilyloxy)-butadiene (Danishefsky's diene) **(12b)** with 2,3-dimethyl-5-oxocyclopent-1-ene-1-carboxylate **(32)** is the key step in the synthesis of the 4-epi-pinguisone **(33),** a member of a class of sesquiterpenes, all of which have a six–five bicyclic structure with the three adjacent methyl groups in a *cis* configuration (Scheme 5.3) [13]. Whereas thermal cycloaddition occurred in low yield with no improvement observed by Lewis-acid catalysis, the yield was greatly improved using high pressure (13 kbar). In this case, cycloaddition, followed by hydrolysis of the intermediate silyl enol ether, gave a 4:1 mixture of enones **34** and **35** in good

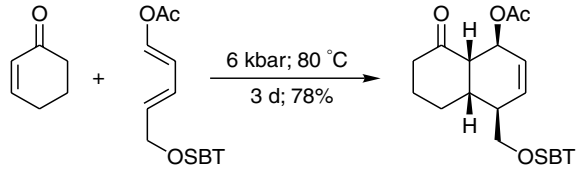


32 **12b** **34** **35** **36** **33**

Scheme 5.3

yield (55 %) together with a 30 % yield of **36**. The enone **34** was then converted into 4-epi-pinguisone **(33)**.

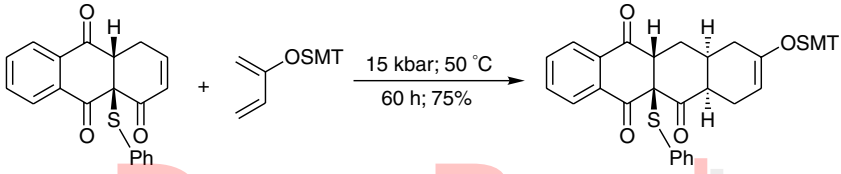
Diels–Alder reaction of 2-cyclohexen-1-one **(37)** with diene **38** mainly afforded the *exo* adduct **39,** the key intermediate in the synthesis of the 'bottom half' of chlorothricolide [14] (Equation 5.4).



(5.4)

37 **38** **39**

Similarly, cycloaddition of the cyclohexenone-like dienophile **40** with 2-trimethylsilyloxy-1,3-butadiene **(41)** allowed [7]: the regio- and stereoselective synthesis of tetracyclic compound **42**, in high yield (Equation 5.5).



(5.5)

40 **41** **42**

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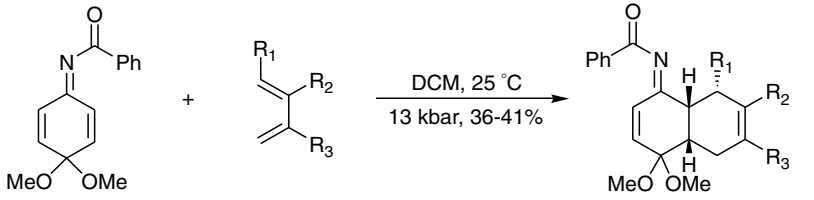
N-Benzoyl-1-amino-*p*-benzoquinone-4-dimethylketal **43** is an interesting starting substrate for the Diels–Alder-based synthesis of alkaloids [15]. The lability under typical Diels–Alder conditions, namely high temperatures and/or Lewis acids, precluded its use as dienophile. Compound **43**, however, reacted with a variety of butadienes **44** under high pressure conditions at room temperature, leading to high yields of cycloadducts **45** that were converted into either annulated benzanilides or naphthanilides by being treated with *p*-toluenesulfonic acid [16] (Equation 5.6). The sequence of cycloaddition followed by aromatization allows the acylated quinone imine ketal to function as a synthetic equivalent of an aminobenzyne.

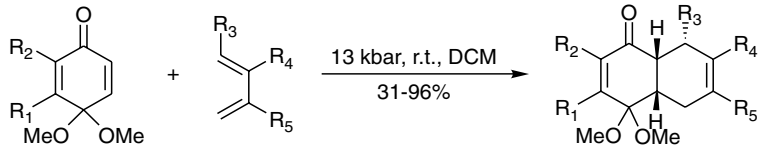


(5.6)

43 **44** **45**

R_1, R_2, R_3= H, Me, OMe, OSMT, OSMDBT

Quinone-mono-ketals **46** and **47** are also low reactive dienophiles and are sensitive to Lewis-acid catalysts. The use of high pressure overcomes this limitation [17]. As shown in Equation 5.7, cycloadditions with a variety of substituted 1,3-butadienes **48** occur regioselectively and *endo*-diastereoselectively in reasonable to good yields. This approach provides access to a variety of annulated benzenes and naphthalenes after aromatization of adducts **49**.



(5.7)

46 R_1= Et, R_2= H

47 R_1= Me, R_2= H

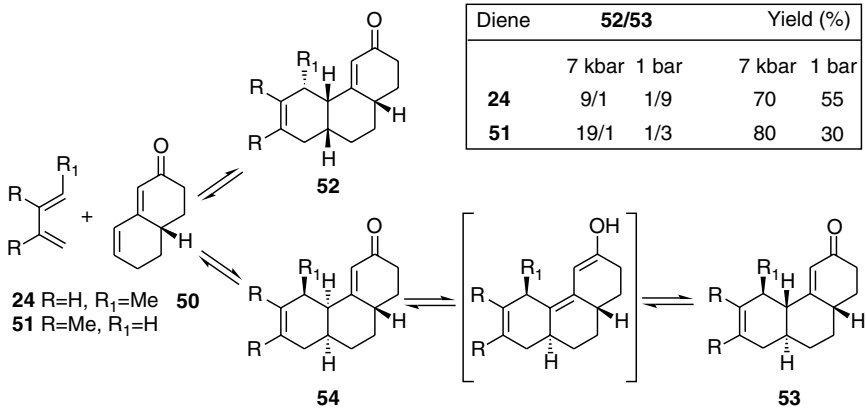
48

49

R_3, R_4, R_5= H, Me, Ph, OSBT

An example of stereocontrol by high pressure is given by the regio- and diastereoselective synthesis of hydrophenanthrenones [18] which are useful intermediates for synthesizing diterpenes and steroids, by $EtAlCl_2$-catalyzed cycloadditions of heteroannular bicyclic dienone **50** with (E)-piperylene **(24)** and 2,3-dimethyl-1,3-butadiene **(51)** (Scheme 5.4).

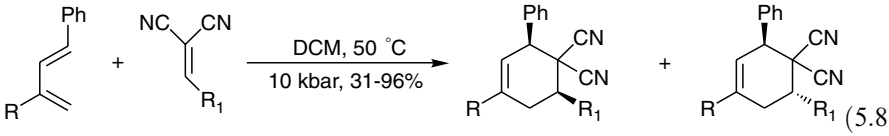
The different ratios of **52/53** produced by cycloadditions performed at atmospheric and high pressure, and the formation of the unusual *trans* adducts **53**, have been explained by the facts that (i) Diels–Alder reactions under atmospheric pressure are thermodynamically controlled, and (ii) the *anti-endo* adducts **52** are converted into the short-lived *syn-endo* adducts **54** which tautomerize (via a dienol or its aluminum complexes) to **53**. The formation of *trans* compounds **53** by induced post-cycloaddition isomerization makes the method more flexible and therefore more useful in organic synthesis.



Diene	52/53		Yield (%)	
	7 kbar	1 bar	7 kbar	1 bar
24	9/1	1/9	70	55
51	19/1	1/3	80	30

Scheme 5.4

A study [19] of the cycloaddition between substituted (E)-1-phenyl-1,3-butadienes **55** and substituted 1,1-dicyanoethylenes **56** leading to *cis*- and *trans*-cyclohexenes **57** and **58** (Equation 5.8) has shown that diastereoselectivity is markedly dependent on pressure.

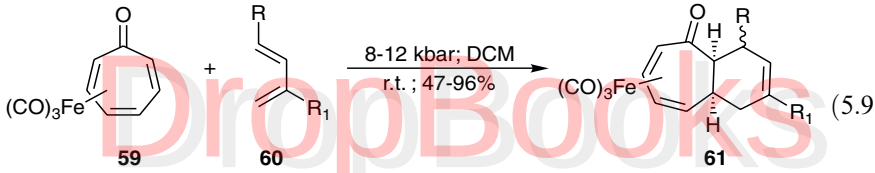


(5.8)

55 **56** **57** **58**

R= Me, Et, *i*-Pr R_1= Me, Et, *i*-Pr, *t*-Bu

Whereas tropones usually act as dienes in cycloaddition reactions (Section 5.4), tricarbonyl (tropone) iron **59** displays a reactivity that is almost identical to that of a normal enone. High pressure cycloadditions of **59** with 1-oxygen substituted dienes **60** gave the desired cycloadducts **61** in good to excellent yields (Equation 5.9). The subsequent decomplexation of the cycloadducts has been accomplished by treatment with CAN [20].



(5.9)

59 **60** **61**

R, R_1= OAc, OSMT, $OCOC_6H_3$-3,5$(NO_2)_2$

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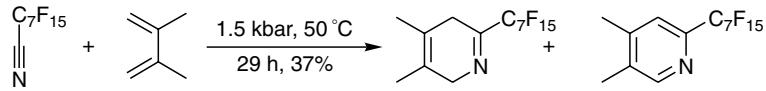
5.2.2 Cycloadditions with Heterodienophiles

Hetero-Diels–Alder reaction is a powerful methodology in the synthesis of heterocyclic compounds. Using the high pressure technique has greatly extended the synthetic applications of this methodology.

Hetero-Diels–Alder reaction of perfluorooctanonitrile **(62)** and 2,3-dimethyl-1,3-butadiene **(51)** allows [21] 3,4-dimethyl-6-perfluoroheptyl-2,5dihydropyridine **(63)** to be synthesized (Equation 5.10). Usually, perfluorocarbon-substituted nitriles require high temperatures to undergo Diels–Alder cycloaddition [22] but, under these conditions, the dihydropyridines gradually eliminate hydrogen and are converted into the corresponding pyridines. Therefore the cycloadducts can be obtained under mild conditions. High pressure (1.5 kbar) cycloadditions between **62** and **51** at 50 °C afforded a mixture of mostly dihydropyridine **63** with the corresponding pyridine **64** (Equation 5.10). The best result (**63**/**64** = 3.7:1) was obtained with a reaction time of 29 h.



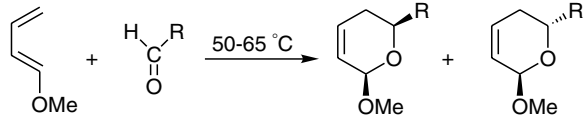
(5.10)

62 **51** **63** **64**

Pyran derivatives, useful intermediates in the total synthesis of many monosaccharides and other natural products, have been synthesized by *hetero*-Diels–Alder reaction by using carbonyl compounds as dienophiles [9, 23].

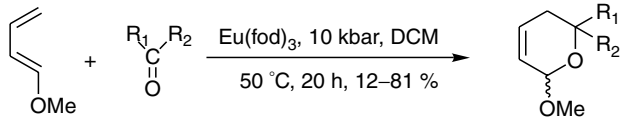
A convenient synthetic route to obtain these compounds is the thermal Diels–Alder cycloaddition of 1-methoxybutadiene **(18b)** with carbonyl compounds, but this route is limited to aldehydes activated by an electron-withdrawing substituent. Non-activated carbonyl compounds require drastic conditions or fail to react. Application of high pressure overcomes this limitation.

Cycloaddition reactions of the simple alkyl and aryl aldehydes **65** with (E)-1-methoxy-1,3-butadiene **(18b)** under high pressure conditions afforded adducts **66** and **67** in reasonable to good yields [2g, 23]. A marked preference for the *endo*-diastereoselectivity has been observed; as usual, applying pressure enforces *endo*-addition (Scheme 5.5). Using mild Lewis-acid catalysts [24], such as $Eu(fod)_3$, $Yb(fod)_3$, or $Eu(hfc)_3$, in combination with pressure, allows good results to be obtained with the added advantage of reducing the pressure to 10 kbar [25] (Scheme 5.5).



18b **65** **66** **67**

R	P (Kbar)	**66/67**	Yield (%)	P (atm)	**66/67**	Yield (%)
Me	20	2.3	65	1	0.45	2
n-C_5H_{11}	14	3.5	28	1	0	0
Ph	19	3	80	1	1	40
2-Fu	19.5	2.7	73	1		



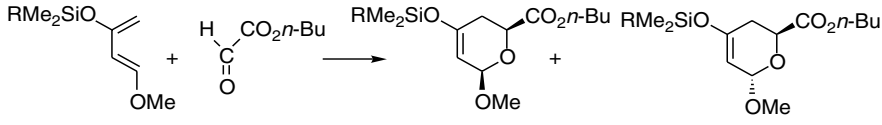
18b **68** *endo*/*exo* = 6/4, 3/7

R_1 = H, Me

R_2 = Me, Ph, 2-Fu, CO_2Me, CH(Me)OSMDBT

Scheme 5.5

More functionalized 5,6-dihydro-2H-pyran-derivatives **71** and **72** have been prepared [26] by cycloaddition of 1-methoxy-3-trialkylsilyloxy-1,3-butadienes **69** with *t*-butylglyoxylate **(70)** (Scheme 5.6). Whereas thermal reactions did not occur in good yields because of the decomposition of the cycloadducts, application of pressure (10 kbar) allowed milder conditions to be used, which markedly improved the reaction yields. The use of high pressure also gives preferentially *endo*-adduct allowing a stereocontrolled synthesis of a variety of substituted 5,6-dihydro-2H-pyran-derivatives, which are difficult to prepare by other procedures.



69 **70** **71** **72**

R	10 kbar, r.t., 24 h		1 bar, 80 °C, 2d	
	Yield (%)	**71**/**72**	Yield (%)	**71**/**72**
Me	80	5	40	1
t-Bu	85	10	30	4

Scheme 5.6

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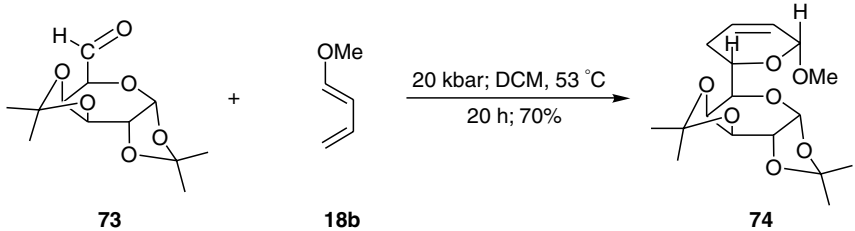
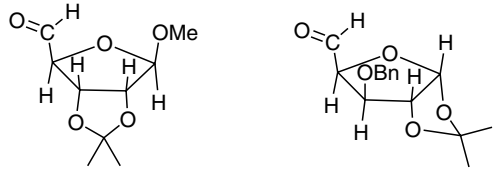
Pressured cycloaddition of (E)-1-methoxybutadiene **(18b)** with 1:2,3:4-di-O-isopropylidene-α-D-galactopyranos-6-ulose **(73)** diastereoisomerically afforded pure cycloadduct **74**, that exhibits the *cis* arrangement of the methoxy group with respect to the sugar moiety [27] (Scheme 5.7). Similar results were obtained with the sugar aldehydes **75** and **76**.



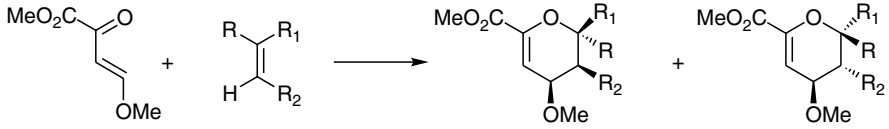
73 **18b** **74**



75 **76**

Scheme 5.7

Table 5.2 High pressure Diels–Alder reactions of diene **77** with dienophiles **78**



77 **78** **79** **80**

R	R_1	R_2	Reaction conditions	**79/80**	Yield (%)
H	OEt	H	PhMe, 110 °C	1.8	48
			$TiCl_4$, DCM, −78 °C	0.3	61
			13 kbar, neat, 24 °C	5.7	82
H	OBn	Me	PhH, 80 °C	3	11
			$EtAlCl_2$, DCM, −78 °C	6	46
			9.5 kbar, DCM, 24 °C	19	50
OMe	OMe	H	DCM, 40 °C	—	63
			13 kbar, DCM, 25 °C	—	41
OMe	OMe	OMe	9.5 kbar, DCM, 24 °C	0.5	41

An alternative approach to the synthesis of pyran derivatives based on high pressure accelerated intermolecular inverse electron-demand Diels–Alder reaction of 1-oxo-1,3-butadienes has been developed by Boger and Robarge [28, 29]. Central to the development of this approach was the selection of appropriately matched diene–dienophile partners of the inverse electron-demand cycloaddition which permits the preparation of carbohydrates bearing a full range of selectively protected oxygen substituents. Methyl-*trans*-4-methoxy-2-oxo-3-butenoate **(77)** and methyl-*trans*-4-phenyl-2-oxo-3-butenoate **(81)** underwent cycloaddition reactions with a variety of electron-rich dienophiles. Some of the results are summarized in Tables 5.2 and 5.3. All the reactions were totally regioselective and, although thermal and catalyzed cycloadditions preferentially proceed through an *endo* transition state, the pressure-promoted cycloadditions are more *endo*-diastereoselective and give higher reaction yields.

Table 5.3 High pressure Diels–Alder reactions of diene **81** with dienophiles **78**

81 **78** **82** **83**

R	R_1	R_2	Reaction conditions	**82/83**	Yield (%)
H	OEt	H	PhMe, 80 °C	4	73
			$EtAlCl_2$, DCM, −78 °C	0.4	94
			6.2 kbar, neat, 24 °C	9	86
H	OBn	Me	6.2 kbar, DCM, 24 °C	25	78
OMe	OMe	H	DCM, 40 °C	—	—
			6.2 kbar, DCM, 24 °C	—	65
OMe	OMe	OMe	10 kbar, DCM, 24 °C	1	72

5.3 OUTER-RING DIENES

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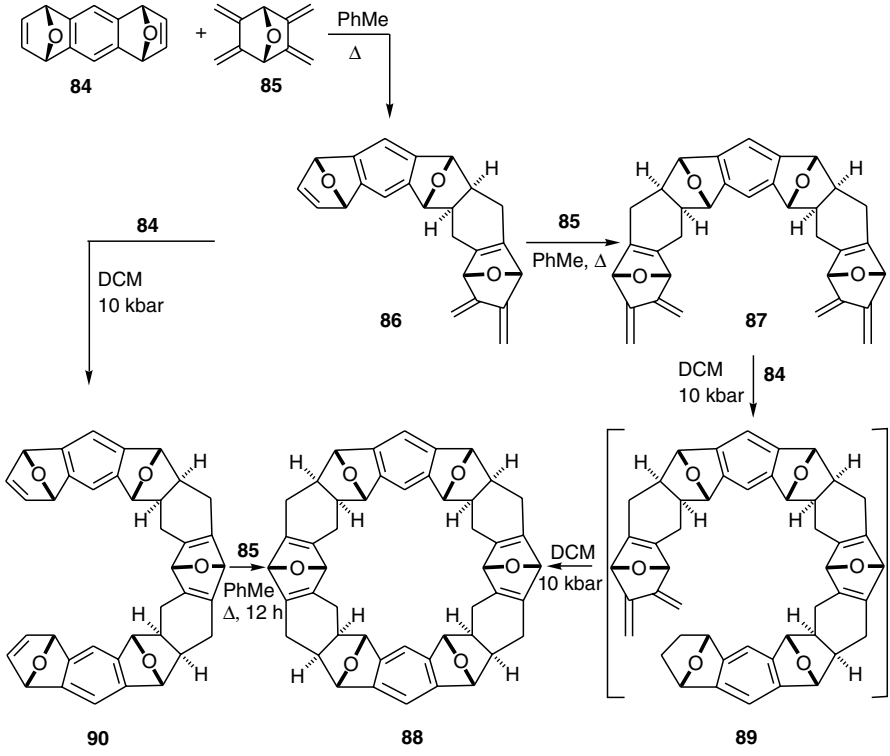
Pressure-promoted stereoregular Diels–Alder reactions have been used in the synthesis of macropolycycles by Stoddart and coworkers [30]. A key feature inthis synthetic approach has been the development of a repetitive Diels–Alder reaction sequence in which three distinct levels of diastereoselectivity are achieved during each cycloaddition involving bisdiene and bisdienophile building blocks. The development of this highly efficient synthesis provided an easy entry into a new series of exotic hydrocarbons. The synthesis of the [12]-cyclacene derivative **88** is a representative example (Scheme 5.8). The chosen building blocks **84** and **85** have diastereotopic π-faces and therefore, in principle, there are eight different ways of interaction. However, the π-facial diastereoselectivities exhibited in cycloadditions with **84** and **85** are such that Diels–Alder reaction occurs preferentially at the *exo*-face of bisdienophile **84** and the *endo*-face of the bisdiene **85**. Thermal equimolecular cycloaddition between **84** and **85** diastereoselectively afforded a mixture of **86** (24 %) and **87** (61 %); the 2:1 adduct **87** is formed from **86**. High pressure-promoted cycloaddition (10 kbar) of **87** with bisdienophile

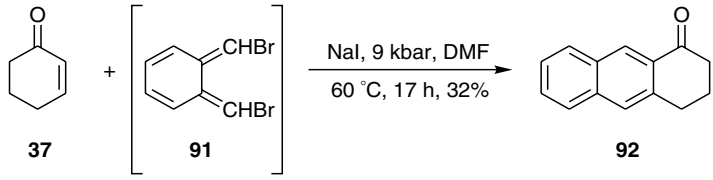
84 led to the desired [12]-cyclacene **88**. The cycloaddition presumably affords the intermediate **89** which immediately undergoes a rapid intramolecular ring closure. In a different approach to **88**, cycloadduct **86** reacted with bisdienophile **84** at high pressure (10 kbar) to afford nonacene **90** (Scheme 5.8). Thermal intermolecular Diels–Alder reaction of **90** with bisdiene **85,** followed by the intramolecular ring closure of the cycloadduct, led to compound **88**.



Scheme 5.8

The *o*-quinodimethanes are very reactive, unstable dienes, which are usually prepared *in situ*. The cycloaddition under high pressure of the dibromo-*o*-quinodimethane **91**, generated *in situ* from α,α,α′,α′-tetrabromo-*o*-xylene,

with 2-cyclohexenone **(37)** directly afforded [31a] 1-(2H)-anthracenone **(92)**, which is a useful starting material for the synthesis of polycyclic aromatic hydrocarbons (Equation 5.11). No reaction occurred under thermal conditions because of the low reactivity of 2-cyclohexenone **(37)**. This one-pot synthesis of **92** is easier than the previously reported four-step synthesis [31b].



37 **91** **92** (5.11)

5.4 INNER-OUTER-RING DIENES

Arylethenes are 'inner-outer-ring dienes' in which the vinyl group is linked to an aromatic system. These dienes are poorly or moderately reactive; the presence of electron-donating substituents in the diene moiety markedly increases their reactivity. Their cycloadditions are usually accelerated in order to be carried out under mild conditions. 1-Vinylnaphthalene is more reactive than 2-vinylnaphthalene and styrenes.

Enantiomers (M)- and (P)-helicenebisquinones [32] **93** have been synthesized by high pressure Diels–Alder reaction of homochiral (+)-(2-*p*-tolylsulfonyl)-1,4-benzoquinone **(94)** in excess with dienes **95** and **96** prepared from the common precursor **97** (Scheme 5.9). The approach is based on the tandem [4 + 2] cycloaddition/pyrolitic sulfoxide elimination as a general one-pot strategy to enantiomerically enriched polycyclic dihydroquinones. Whereas the formation of (M)-helicene is explained by the *endo* approach of the arylethene toward the less encumbered face of the quinone, the formation of its enantiomeric (P)-form can be the result of an unfavourable interaction between the OMe group of approaching arylethene and the sulfinyl oxygen of **94**.

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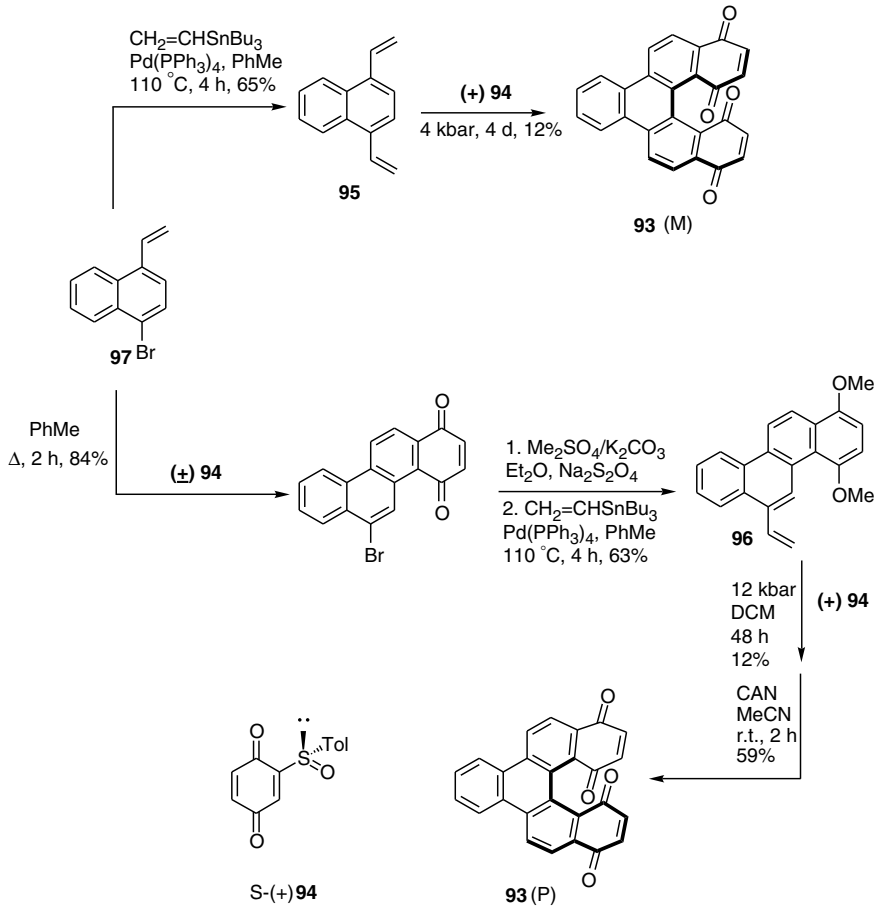
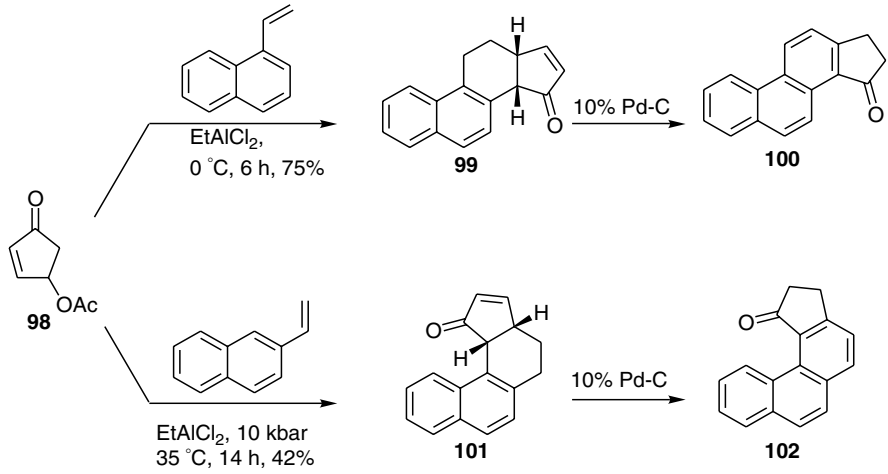


Scheme 5.9

Although 1-vinylnaphthalene thermally reacts with 4-acetoxy-2-cyclopenten-1-one **(98)** to regioselectively afford **99**, the isomer 2-vinylnaphthalene gives the same thermal cycloaddition with low yield (30 %) and reacts satisfactorily only with **98** at 10 kbar (Scheme 5.10). Both products **99** and **101** were converted into the cyclopenta[a]phenanthren-15-one **(100)** and cyclopenta[c]phenanthren-1-one **(102)** isomers. Acetoxyketone **98** acts as a synthetic equivalent of cyclopentadienone (**114** in Scheme 5.14) in cycloaddition reactions [33].



Scheme 5.10

Since dihydroarylethenes are more reactive than the corresponding fully aromatic compounds, their use in the cycloaddition reactions is preferred in order to carry out the reactions under mild conditions with higher yields. Some reactions of 3,4-dihydro-1-vinylnaphthalene **(103)** [33], 3,4-dihydro-2-vinylnaphthalene **(104)** [34], and 1,2-dihydro-4-vinylphenanthrene **(105)** [35] with 4-acetoxy-2-cyclopentenone **(98)** and 2-inden-1-one **(106)** are summarized in Schemes 5.11–5.13.

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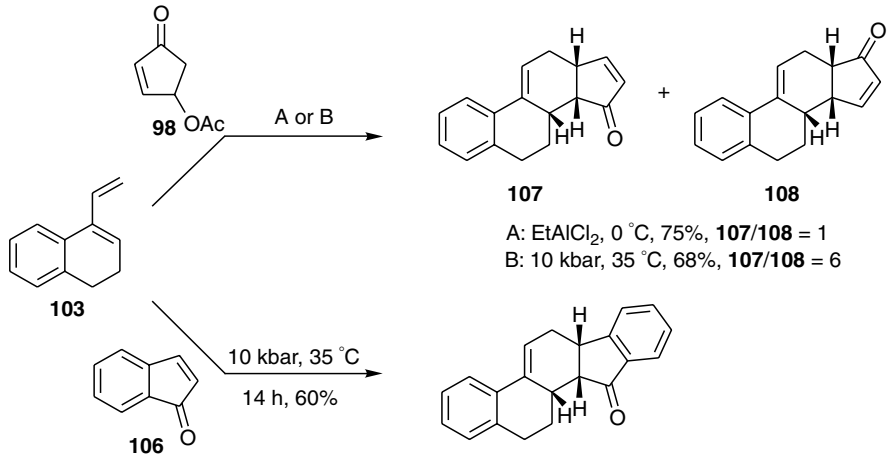
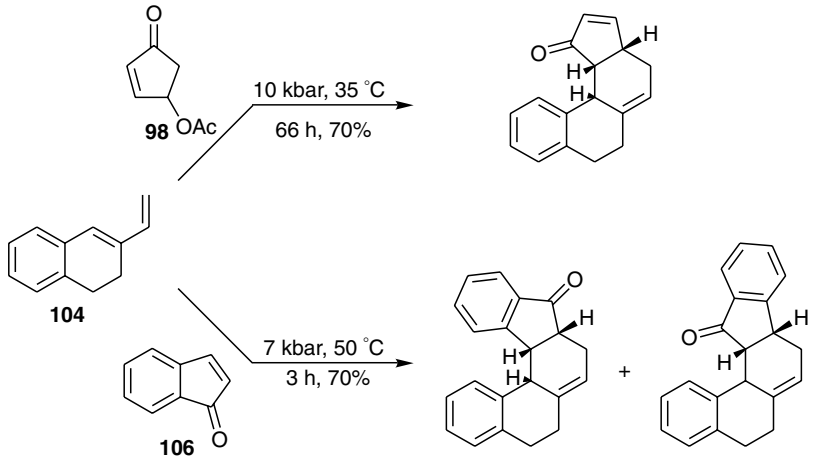
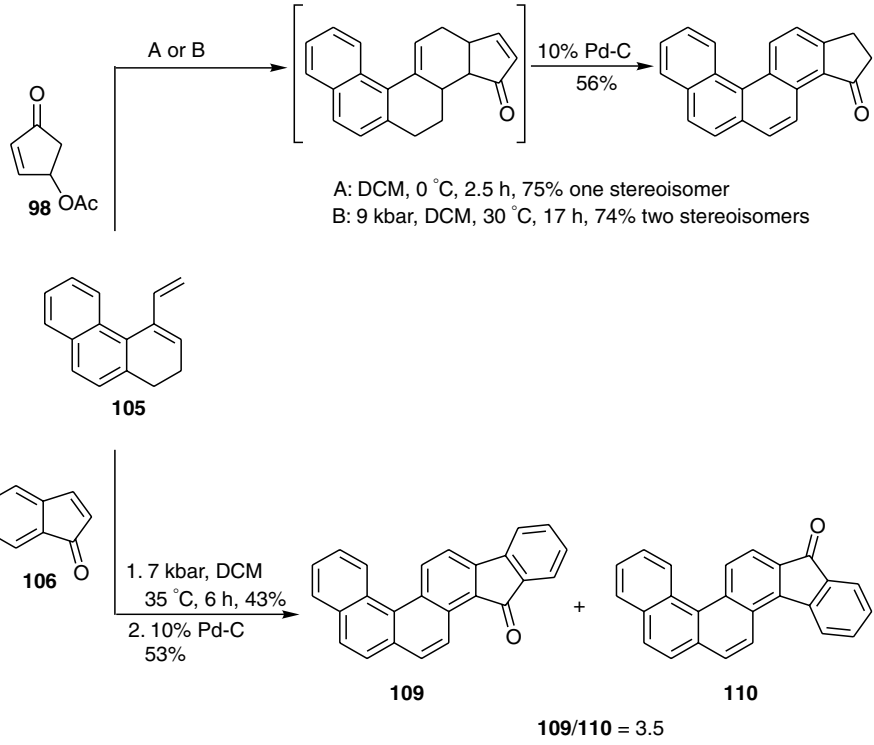


Scheme 5.11



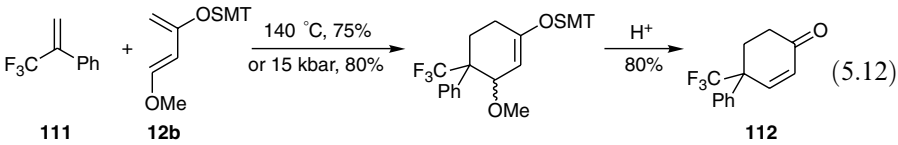
Scheme 5.12

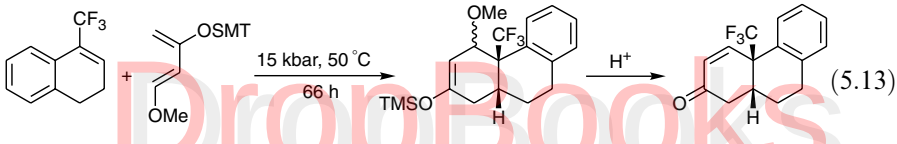


Scheme 5.13

Pressure influences the regioselectivity and the *endo–exo* diastereoselectivity of the cycloadditions. All the cycloadducts were converted into polycyclic aromatic hydrocarbons by treatment over a Pd/charcoal catalyst. This approach provides a new and efficient route to a broad variety of polycyclic aromatic hydrocarbons [36].

When electron-withdrawing groups are introduced at the vinyl moiety, arylethenes may behave as dienophiles. Thus α-trifluoromethyl styrene **(111)** interacted with Danishefsky's diene **(12b)** under thermal or high pressure conditions [37] to regioselectively afford a 1:1 mixture of cycloadducts which were then converted to 4-phenyl-4-trifluoromethyl-2-cyclohexen-1-one **(112)** (Equation 5.12). A direct access to angularly trifluoromethyl-substituted tricyclic compounds may be achieved by cycloaddition of the 1-trifluoromethyl-3,4-dihydronaphthalene **(113)** with diene **12b** (Equation 5.13).





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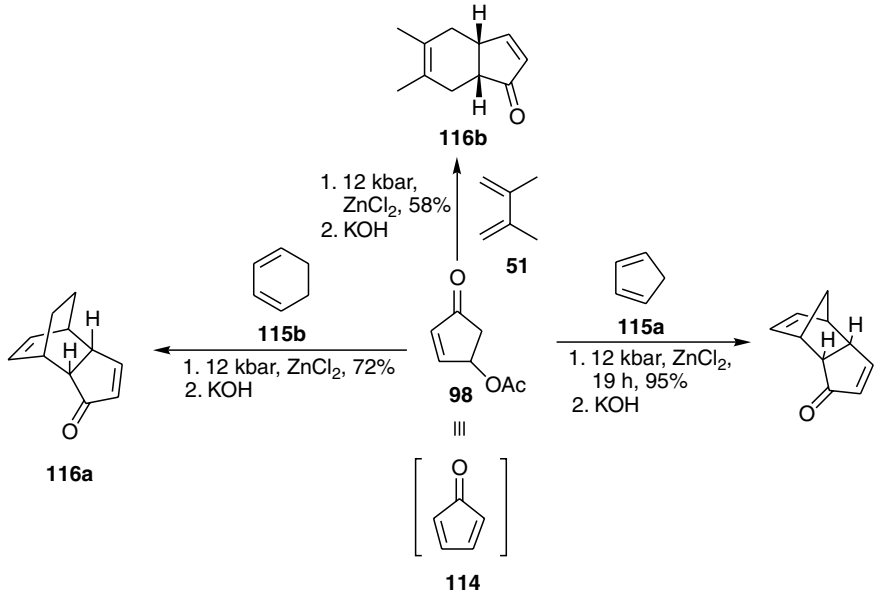
5.5 INNER-RING DIENES

5.5.1 Cyclopentadienes and Cyclohexadienes

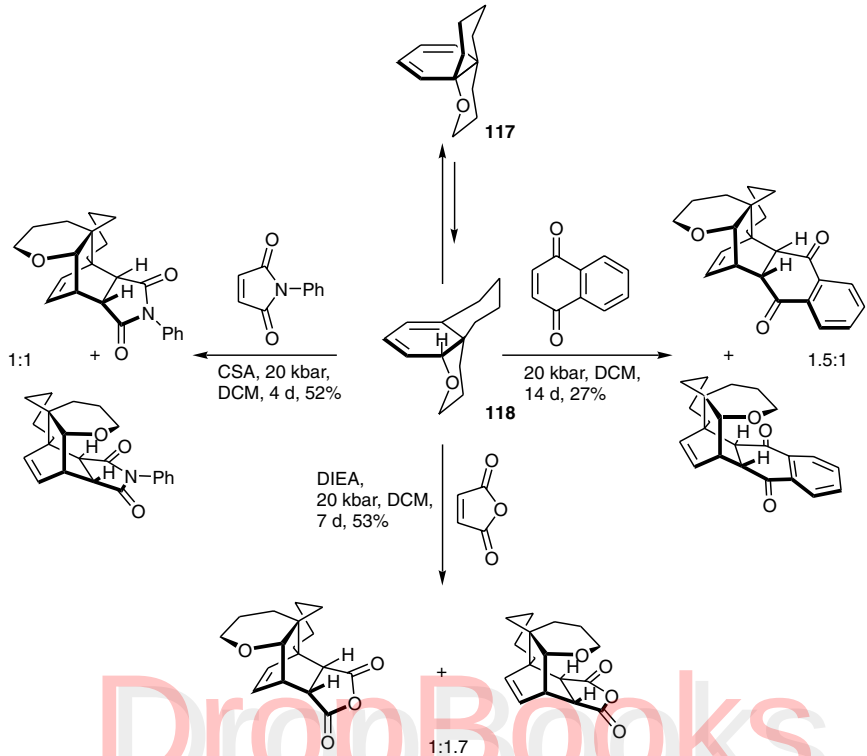
4-Acetoxy-2-cyclopenten-1-one **(98)** is an interesting dienophile that acts as a synthetic equivalent of cyclopentadienone **(114)** [38]. Ketone **98** is poorly reactive; whereas it underwent cycloaddition reactions with reactive cyclic dienes, such as cyclopentadiene **(115a)** using zinc chloride as catalyst, it did not react with less reactive dienes such as 1,3-cyclohexadiene **(115b)** and 2,3-dimethyl-1,3-butadiene **(51)**. At 12 kbar and using zinc chloride as catalyst, both dienes underwent a smooth reaction (Scheme 5.14) [39]. Treatment of the reaction mixtures with 1N KOH afforded *endo*-tricyclo [5.2.2.0[2,6]] undecadienone **(116a)** and dimethyl tetrahydroindenone **(116b),** in 72 % and 58 % overall yield, respectively; these are suitable synthons for a variety of natural products.



Scheme 5.14

An interesting phenomenon has been observed in the high pressure Diels–Alder reactions of the 1-oxa[4.4.4]propella-5,7-diene **(117)** with 1,4-naphthoquinone, maleic anhydride and N-phenylmaleimide, where the diene **117** undergoes a rearrangement to the diene isomer **118** which, although thermodynamically less favored, exhibits a greater reactivity [40]. The reactivities of the three dienophiles differed since maleic anhydride and N-phenylmaleimide reacted only in the presence of diisopropylethylamine (DIEA) and camphorsulfonic acid (CSA), respectively (Scheme 5.15). The distribution of the adduct pairs shows that the oxygen atom does not exert a consistent oriental dominance on π-facial selectivity.

Cycloalkenones and/or their derivatives can also behave as dienic partners in the Diels–Alder cycloaddition. It is well documented [41] that cyclic acetals, for example, can interconvert with ring-opened enol ether forms, in a reversible manner; the latter compounds can then be trapped by various dienophiles. Thus dienes **119** and **120** reacted with [60]-fullerene (C_{60}) at high pressure, affording highly thermally stable products [42] (Scheme 5.16). Ketones **123** and **124** could be directly obtained by cycloaddition of enol forms **121** and **122** of 2-cyclopenten-and 2-cyclohexen-1-one, respectively.



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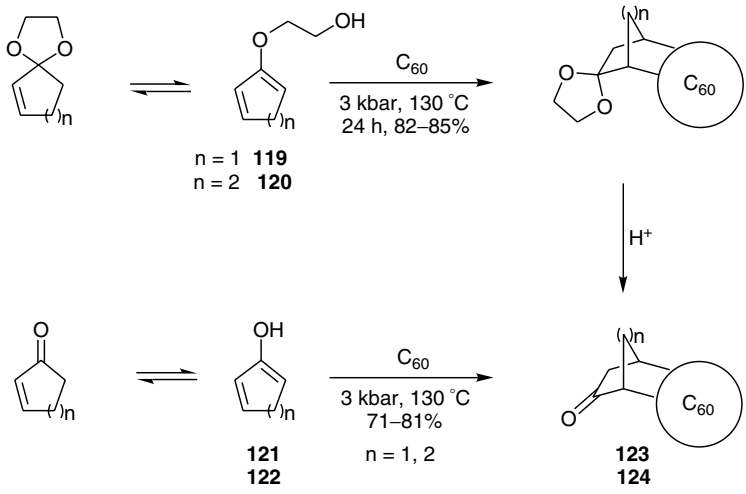
Scheme 5.15

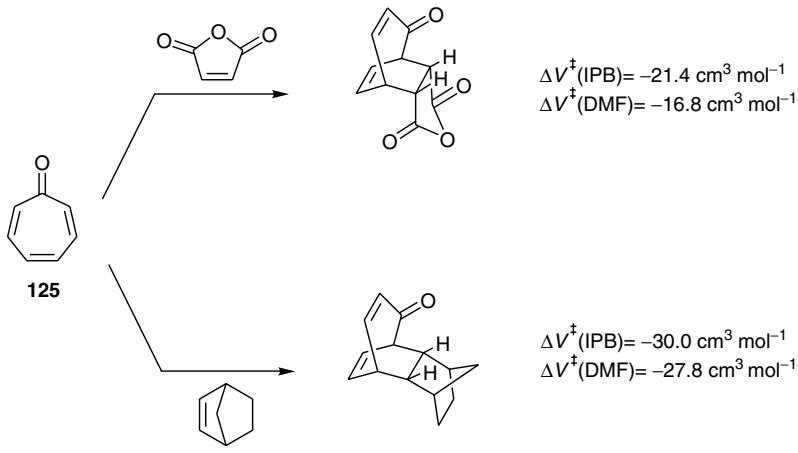


Scheme 5.16

5.5.2 Tropones as Dienes

Tropones are non-benzenoid compounds that behave like 4π-components in a Diels–Alder reaction. These compounds are of interest because of their synthetic applications based on the Diels–Alder reaction, since the cycloadducts can be easily converted into a large variety of compounds.

The study of high pressure cycloaddition reactions of tropone **(125)** with maleic anhydride and norbornene allowed the reaction activation volumes to be measured and showed that they are large, negative and solvent-dependent (Scheme 5.17) [43a].


125
$\Delta V^{\ddagger}$(IPB)= –21.4 cm^3 mol^{-1}
$\Delta V^{\ddagger}$(DMF)= –16.8 cm^3 mol^{-1}
$\Delta V^{\ddagger}$(IPB)= –30.0 cm^3 mol^{-1}
$\Delta V^{\ddagger}$(DMF)= –27.8 cm^3 mol^{-1}

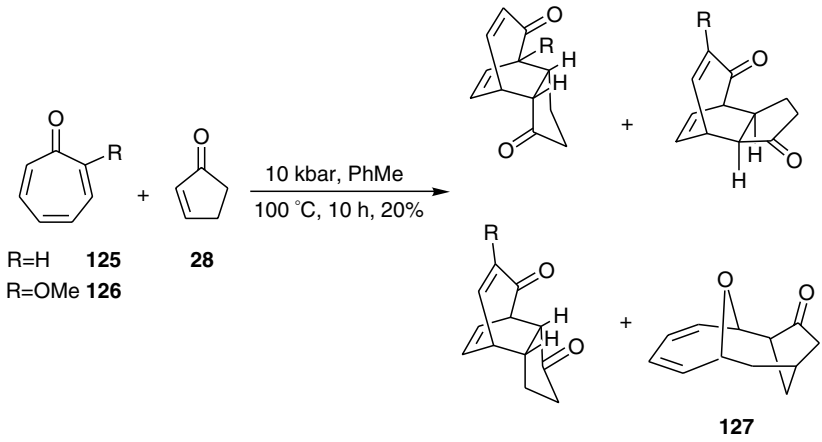
Scheme 5.17

Tropone **(125)** and the 2-substituted tropones showed a different reactivity in the cycloaddition with 2-cyclopentenone **(28)**. Whereas tropone itself **(125)** and the 2-methoxytropone **(126)** reacted at 10 kbar, giving a mixture of four and three products, respectively (Scheme 5.18), 2-hydroxy- and 2-chloro-tropone failed to react at all [43b]. Compound **127** does not have the expected dihydrohomobarrelenone framework; it is probably derived from the cycloaddition of **125** and 1,4-cyclopentadien-1-ol, the enol form of **28**.

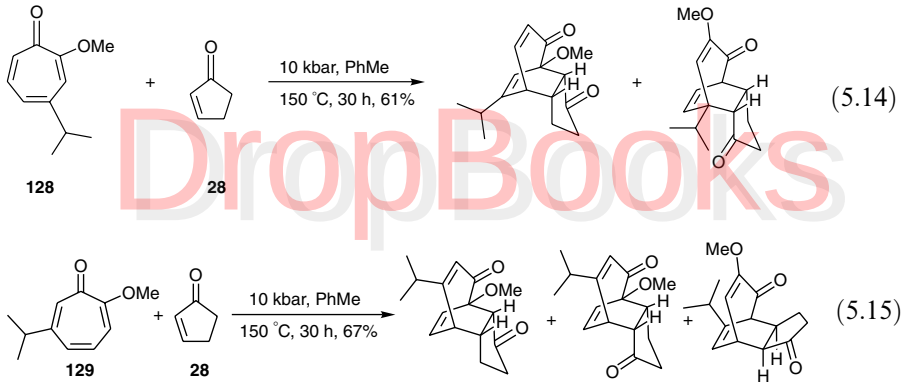
Similar results were obtained in the cycloadditions of 2-cyclopentenone **28** with 2-methoxy-4-isopropyl-tropone **(128)** and 2-methoxy-6-isopropyl-tropone **(129)** (Equations 5.14 and 5.15).

Tropone **(125)** and tropolone **(130)** reacted [44] with N-phenylmaleimide at high pressure (10 kbar) and gave a mixture of *exo*- and *endo*-adducts, **131** and **132,** respectively (Equation 5.16).

Another versatile two-step synthesis of homobarrelenones [45] is based on the high pressure cycloaddition of tropone **(125)** and its 2-methoxy-, 2-hydroxy- and 2-chloro-derivatives with 2,3-bis(methoxycarbonyl)-7-oxabicyclo[2.2.1]hepta 2,5-diene **(133)** followed by thermolysis of the cycloadducts at 130 °C with the



Scheme 5.18



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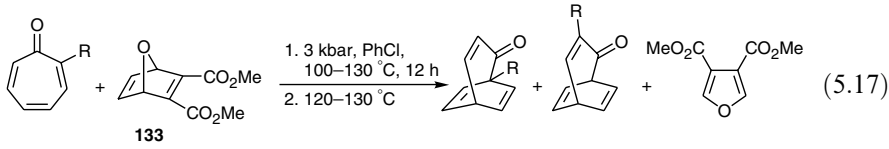
extrusion of the furan ring (Equation 5.17). Diels–Alder adducts of furans are known to readily undergo a cycloreversion reaction; 7-oxabicyclo[2.2.1]heptadiene **133** behaves like a synthetic equivalent of acetylene [46]. Homobarrelenones substituted at the bridgehead carbon rearrange into the indanones.

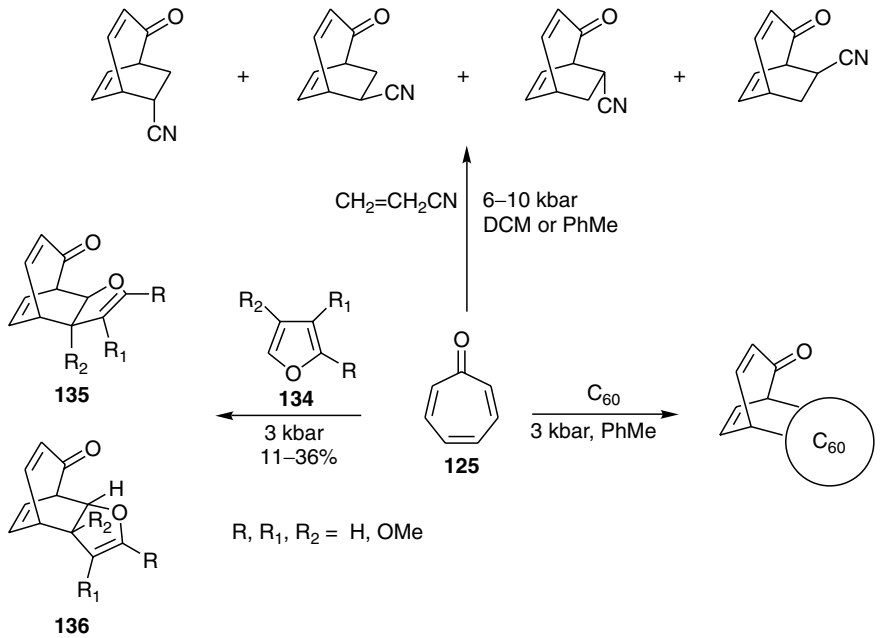


(5.17)

R = H, OMe, OH, Cl

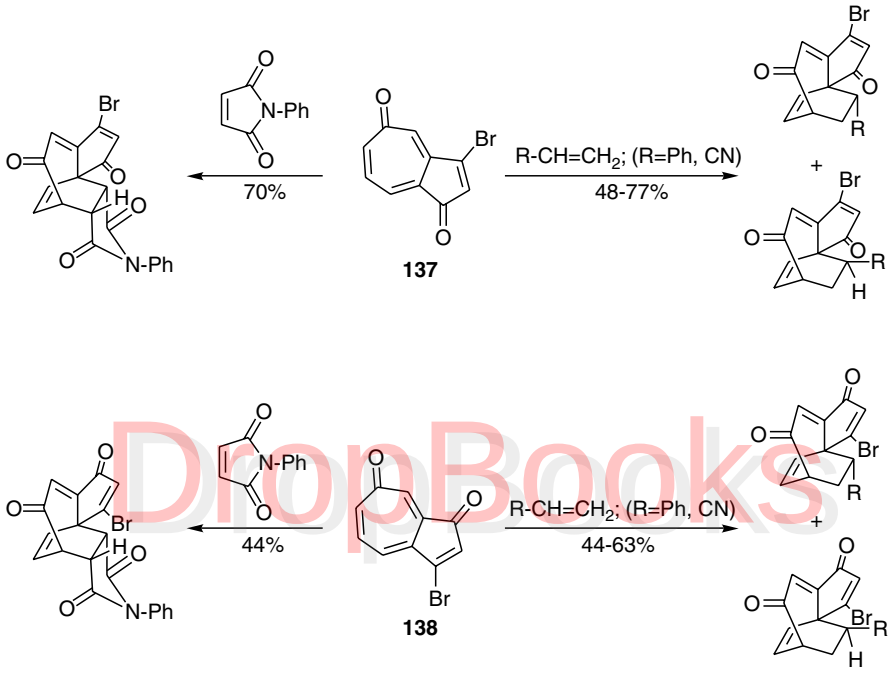
Tropone **(125)** reacted with acrylonitrile under both thermal and high pressure conditions [47] to afford a mixture of regioisomers and *endo–exo* diastereoisomers (Scheme 5.19). The product distribution was not dependent on pressure, but was slightly temperature dependent. There is a sharp preference for *endo*-selectivity.

Cycloaddition of **125** with buckminsterfullerene (C_{60}) at 3 kbar allowed the adduct [48] to be obtained, preventing a retro Diels–Alder process (Scheme 5.19). Cycloadditions of tropone **(125)** with furans **134** gave mixtures of 1:1 *endo*-and *exo*-monocycloadducts **135** and **136**, respectively [49a], together with some bisadducts. In this case furan reacts solely as the 2π component in spite of its diene system. Whereas 2-methoxy furan gave mainly the kinetically controlled product **135** (R= OMe; $R_1 = R_2 = H$), under the same conditions 3,4-dimethoxy furan afforded the thermodynamically controlled cycloadduct **136** (R=H; $R_1 = R_2 = OMe$) as the major product (Scheme 5.19).



Scheme 5.19

Azulene quinones [49b] are compounds related to the family of tropones and are considered to possess great biological and physiological potential. Several polycyclic compounds have been prepared by high pressure (3 kbar, PhCl, 130 °C, 15 h) Diels–Alder reaction of 3-bromo-1,5-azulene quinone **(137)** and 3-bromo-1,7-azulene quinone **(138)** with several dienophiles. The cycloadditions were regioselective and afforded cycloadducts in reasonable to good yields (Scheme 5.20).

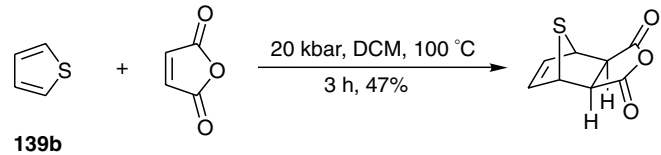


Scheme 5.20

5.5.3 Furans and Thiophenes

Heteroaromatic five-membered compounds, such as furan **(139a)** and thiophene **(139b)**, may be formally considered to be 1,3-butadienes with their terminal carbons 'tied down' by a heteroatom bridge; chemically, they can behave as conjugated dienes. Furan **(139a)** has a low aromatic character and hence it has a great tendency to behave like a conjugated diene. Unlike furan, the more aromatic thiophene **(139b)** is a very poor diene that does not usually undergo the Diels–Alder reaction under thermal and Lewis-acid-catalyzed conditions. It may react with highly reactive dienophiles like dicyanoacetylene and tetrafluorobenzyne to give aromatic compounds; the Diels–Alder cycloadditions of thiophenes are often followed by the loss of the heteroatom. The thiophene derivatives, such

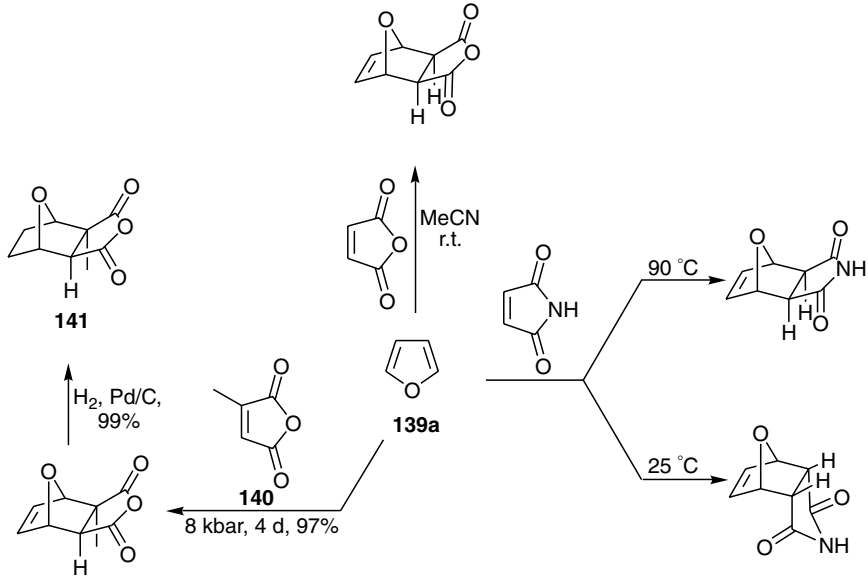
as thiophene-1,1-dioxide and 2,5-dimethoxythiophene, react thermally. However, the reaction of thiophene **(139b)** with maleic anhydride may be promoted by high pressure [50] and leads to the *exo*-cycloadduct, with the yield depending on the reaction temperature, pressure and solvent (Equation 5.18). Under high pressure conditions, the choice of solvent becomes important as is well documented in various studies on the kinetic solvent effects [51]. The best yield was obtained at 100 °C and 20 kbar in dichloromethane.



139b (5.18)

The more reactive furan **(139a)** undergoes thermal Diels–Alder reaction [52] with reactive dienophiles such as maleic anhydride and maleimide (Scheme 5.21). Whereas the cycloaddition with the maleic anhydride afforded the *exo*-adduct at room temperature, the stereochemistry of the reaction of maleimide depends on the reaction temperature.

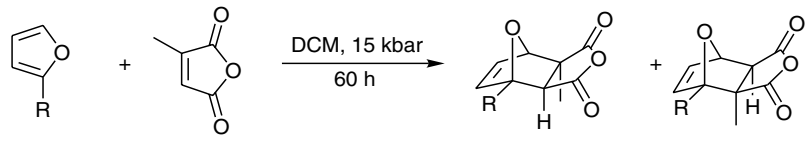
Diels–Alder reactions of furans are markedly reversible because of the aromatic character of the furan nucleus [1a]. The lability of the cycloadducts, even at relatively low temperatures, as well as the sensitivity to acidic conditions of both furans and cycloadducts, preclude the use of strong Lewis acids and have therefore given importance to the high pressure technique.



Scheme 5.21

Whereas maleic anhydride can react with furan **(139a)** at ambient pressure, citraconic anhydride **(140)** reacts only at high pressures due to the strong deactivating effect of the methyl group (Schemes 5.21 and 5.22). The two-step synthesis [53] of the palasonin **(141)**, in an overall yield of 96 %, is a good example of the acceleration of the Diels–Alder by high pressure (Scheme 5.21). Previous synthesis [54] based on the thermal Diels–Alder reaction of furan with methoxy carbonyl maleic anhydride required 12 steps.

High pressure cycloaddition of cytraconic anhydride **(140)** with 2-substituted furans **142** afforded, *exo*-diastereoselectively but unregioselectively, bicyclic cycloadducts **143** and **144** that have been used in straightforward routes to CD-ring fragment of paclitaxel [55] (Scheme 5.22). The cycloadducts were then



142 **140** **143** **144**

R	**143/144**	Yield (%)
Me	1	65
CO_2Et	–	–
CH_2OAc	0.8	59
CH_2OCOt-Bu	1	54
CH_2OBn	1.4	31

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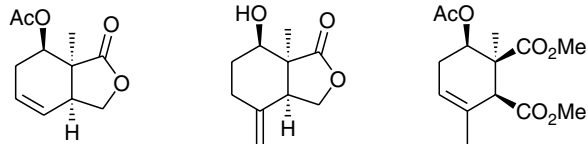
Scheme 5.22

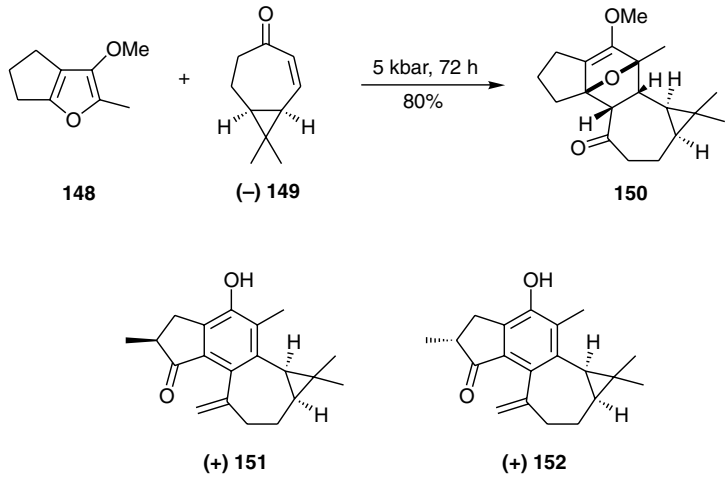
converted into bicyclic lactones **145** and **146** and into cyclohexene derivative **147** (Figure 5.3) which is a potential precursor in the total synthesis of paclitaxel and paclitaxel analogs. The application of high pressure accelerates the formation of cycloadducts **143** and **144**.



145 **146** **147**

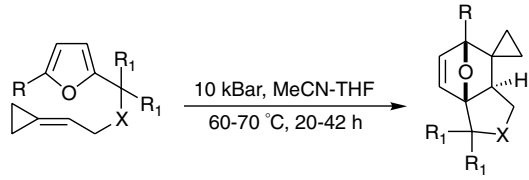
Figure 5.3

Diels–Alder reaction of the furan derivative **148** with homochiral bicyclic enone **149** is the key step [56] in the total synthesis of the diterpenes jatrophalone A and B, **151** and **152**, respectively, isolated from *Jatropha gossypiifolia* L [57]. Initial efforts to carry out the cycloaddition between **148** and **149** under thermal or Lewis-acid conditions failed due to diene instability. Application of 5 kbar of pressure to a neat 1:1 mixture of diene and dienophile afforded crystalline **150** with the desired regiochemistry (Scheme 5.23). Subsequent aromatization, introduction of the methylene group, oxidation and methylation afforded (+)-jatropholones **151** and **152**.



Scheme 5.23

High pressure technique has also been applied successfully to intramolecular Diels–Alder reactions of furan derivatives. Furfuryl-substituted methylene cyclopropane derivatives **153** did not undergo intramolecular cycloaddition under thermal conditions, since tar and polymers were essentially obtained. Lewis-acids, such as $Cu(OAc)_2 \cdot H_2O$, ZnI_2, $LiClO_4$ and $BF_3 \cdot OEt_2$, which have been reported to promote cycloaddition reactions of furan derivatives, failed or were only marginally successful. At high pressure, compounds **153** underwent intramolecular Diels–Alder reaction [58] readily and *exo*-diastereoselectively, leading to new spirocyclopropane tricyclic compounds **154** in good to high yields (Scheme 5.24). In order to quantify the pressure effect on the kinetics, the activation volumes were determined.



153 **154**

X	R	R_1	Yield(%)
O	H	H	>95
O	H	Me	>95
O	Me	H	74
O	OMe	H	>95
NMe	H	H	50
NMe	H	=O	55

Scheme 5.24

The synthesis of phorbols [59] is another representative example of high pressure intramolecular Diels–Alder reaction. Phorbol **155** is a natural product found in croton tiglium oil. Phorbols are biologically active diterpene members of the tiglione family which have a tetracyclic framework. Prostatin **156** (12-deoxyphorbol acetate) is of medical interest due to its cytoprotective effect in human lymphocytic cells infected with HIV-1. A one-pot stereocontrolled construction of the base tricyclic skeleton, having the functionality and stereochemistry inherent in phorbols and its analogs, has been achieved by high pressure mediated intramolecular cycloaddition of compounds having the furane moiety (Scheme 5.25).

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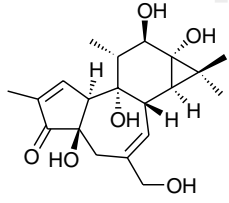

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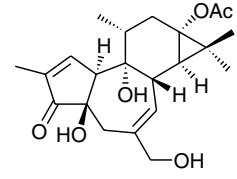

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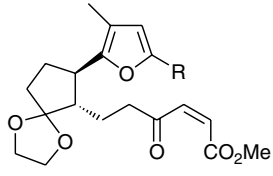
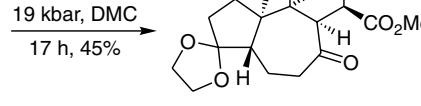


157 **a**, R = SBn
b, R = SPh

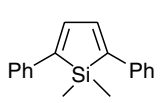


158

Scheme 5.25

Furan derivative **157a** at 19 kbar gave the tricyclic product **158** *endo*-diastereoselectively and in good yield. Disconcertingly, it was found that analog **157b** did not react, thus emphasizing that the nature of the thioether group at the furan nucleus plays a crucial role in the success of the intramolecular process. While the real reason for the reluctance of compound **157b** to undergo cycloaddition remains obscure, the fact that the Diels–Alder reaction is possible with substrate **157a** has opened a route to the total synthesis of phorbol.

Fused norbornene analogs, containing silicon and oxygen atoms in bridgehead positions, have been prepared [60] by high pressure cycloaddition of siloles **159** and **160** with oxanorbornene derivatives **161–164** (Scheme 5.26). These cycloaddition reactions at atmospheric pressure either do not proceed or proceed only at higher temperatures where the starting materials already begin to thermally decompose. The cycloadducts are cavity-shaped silicon-containing polycyclic systems of potential interest for host–guest chemistry.



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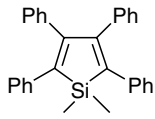

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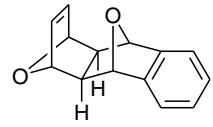

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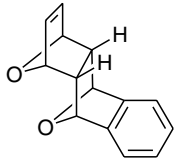

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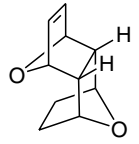

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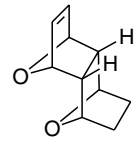


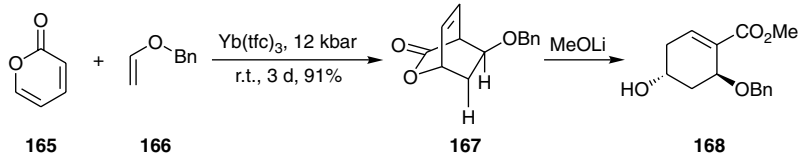
164

Scheme 5.26

5.5.4 Pyrones and Pyridones

Whereas electronically activated 2-pyrones can react thermally in both normal and inverse electron-demand Diels–Alder cycloaddition, 2-pyrone by itself requires thermal conditions that are so vigorous that they cause spontaneous extrusion of carbon dioxide from the bicyclic cycloadduct [61].

Synthon **168**, a direct precursor to ring-A diastereoisomer of 1-hydroxyvitamin D3 analog having selective biological activities, has been synthesized by high-pressure Lewis-acid-catalyzed inverse electron-demand Diels–Alder cycloaddition of the commercially available 2-pyrone **(165)** with benzylvinylether **(166)** [62]. The cycloaddition led regio-and diastereoselectively to bicyclic lactone **167** which was then converted, by methanolysis, to the trisubstituted cyclohexene **168** (Equation 5.19). No cycloaddition occurred at atmospheric pressure or under the influence of the Lewis acid alone, and only low cycloadduct yields were obtained when performing the reaction under high pressure without a Lewis-acid catalyst.



165 **166** **167** **168** (5.19)

A marked dependence of the reaction yield on the nature of the Lewis-acid catalyst and on the diene–dienophile ratio was observed (Table 5.4). 2-Pyrone **(165)** reacted at 18.5 kbar with methylacrylate but the reaction was unregioselective and undiastereoselective.

2-Acetoxypyran-2-one **(169)** reacted with chiral enolethers **170** under high pressure conditions. Diastereofacial selectivities ranged from 52/48 to 88/12 depending on the nature of the dienophile [63] (Equation 5.20).

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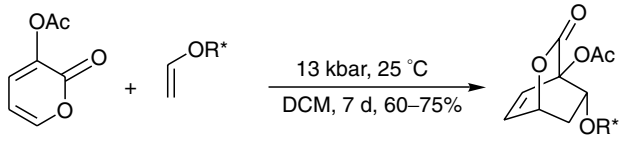
Table 5.4 High pressure Lewis-acid catalyzed Diels–Alder reactions of 2-pyrone **165** with benzylvinylether **166**[a]

Lewis-acid	**166** (equiv.)	Yield (%)
$Yb(tfc)_3$ (homochiral)	2	91
$Yb(fod)_3$	2	72
$Yb(fod)_3$	5	94
$Yb(NO_3)_3 \cdot 5H_2O$	2	31
$Yb(NO_3)_3 \cdot 5H_2O$	5	90
$ZnCl_2$	2	24
$ZnCl_2$	5	73
$ZnCl_2$	5	92[b]

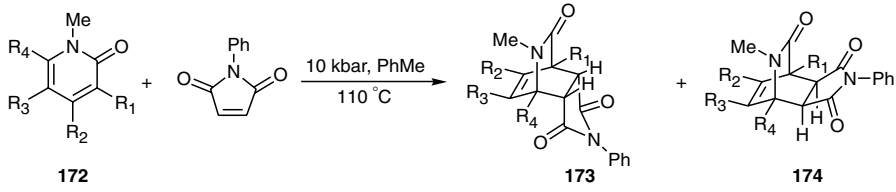
[a] In the absence of solvent.
[b] In DCM at 11–12 kbar.



169 **170** **171** (5.20)

R* = isomenthyl; 2-(α-naphthyl)cyclohexyl; 8-phenylmenthyl; 8-(β-naphthyl)menthyl; 8-(3,5-dimethylphenyl)menthyl.

2-Pyridones have higher aromatic character than 2-pyrones and therefore give Diels–Alder cycloadditions at atmospheric pressure with highly reactive dienophiles or when electron-withdrawing substituents are present in the molecule. The reactions of some phenyl-substituted 1-methyl-2(1H)-pyridones **172** with N-phenylmaleimide under atmospheric and high pressure conditions have been examined in order to open a new efficient route towards isoquinuclidine derivatives [64]. High pressure cycloadditions afforded high yields of mixtures of *endo* and *exo* adducts **173** and **174**, some of which were unobtainable under atmospheric pressure. The *endo–exo* diastereoselectivity is influenced by the pressure (Scheme 5.27).



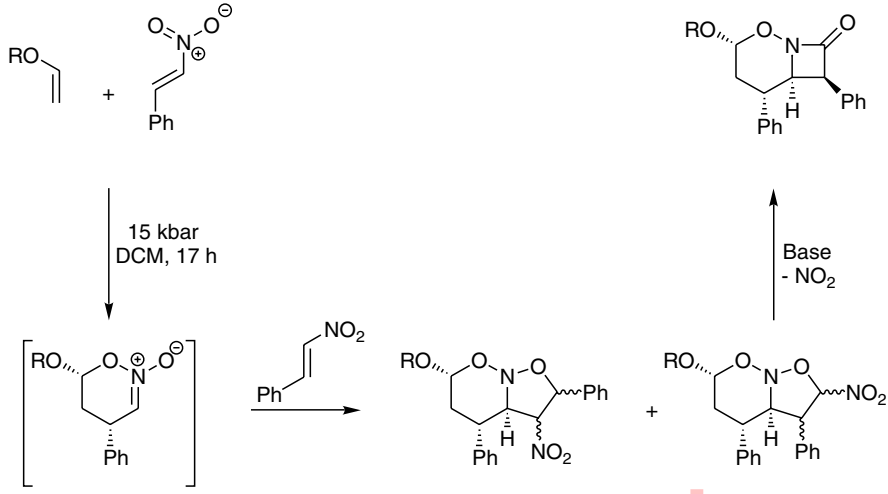
172 **173** **174**

				Yield (%) at 10 kbar		Yield (%) at 1 atm	
R_1	R_2	R_3	R_4	**173**	**174**	**173**	**174**
Ph	H	H	H	26	50	0	0
H	Ph	H	H	11	2	50	0
H	H	Ph	H	78	18	90	0
H	H	H	Ph	76	8	0	0

Scheme 5.27

5.6 OUTLINED DIELS–ALDER REACTIONS

A simple entry towards bi-and tricyclic N-oxy-β-lactams by high pressure promoted tandem [4 + 2]/[3 + 2] cycloadditions of enol ethers and β-nitrostyrene [65]



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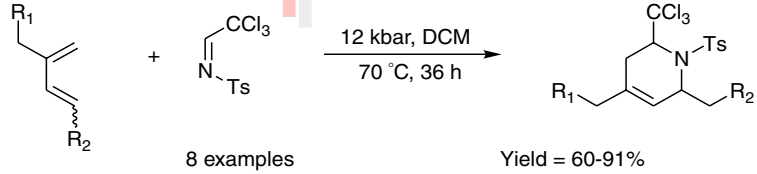
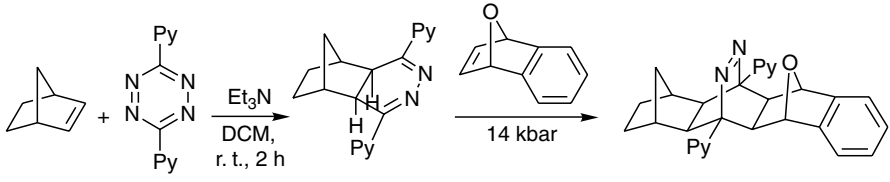
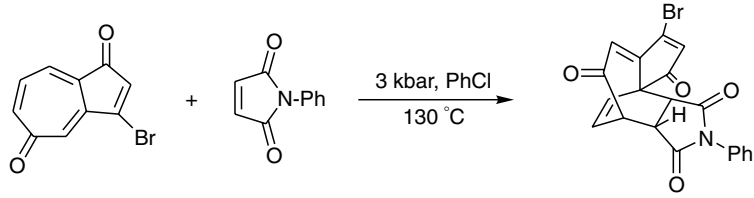
A versatile synthesis of substituted tetrahydropyridines [66]



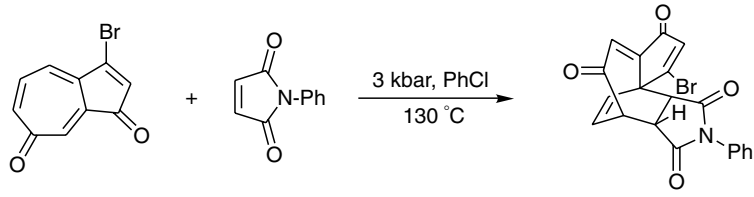
The preparation of rigid alicyclic molecules bearing effector groups from alkene blocks using s-tetrazines and 1,3,4-triazines as stereoselective coupling agents [67]



High-pressure cycloaddition reactions of 3-bromo-1,5-azulenequinone and 3-bromo-1,7-azulenequinone with dienophiles [68]

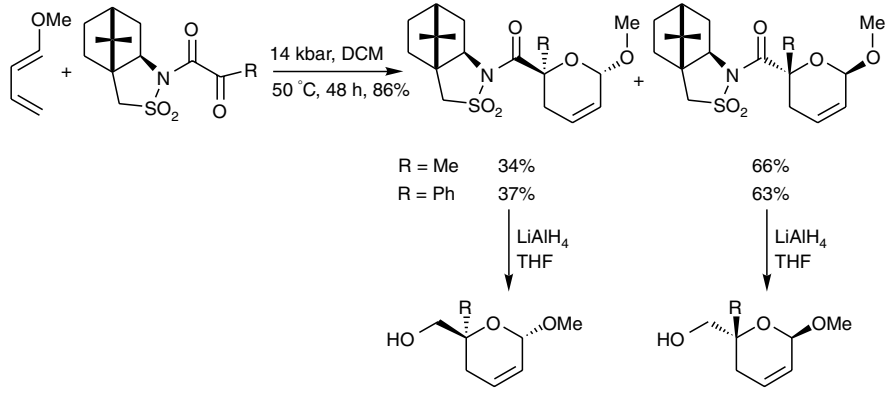


9 dienophiles Yield = 17-80%

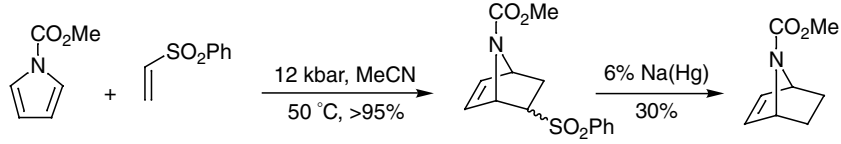


5 dienophiles Yield = 44-64%

Asymmetric *hetero*-Diels–Alder addition of 1-methoxybuta-1,3-diene to (2R)-N-pyruvoyl-and (2R)-N-(phenylglyoxyloyl)bornane-10,2-sultam [69]

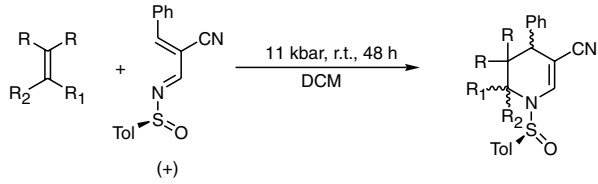


Synthesis and structure-activity data of some new epibatidine analogues [70]



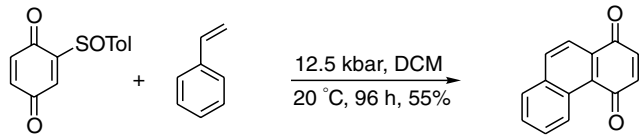
endo/*exo* = 1:1

Synthesis of tetrahydro-and dihydropyridines by *hetero*-Diels–Alder reaction of enantiopure α,β-unsaturated sulfinimines [71]



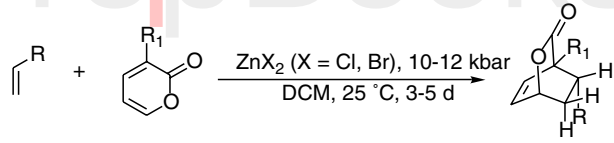
R = H, Me; R_1 = OEt, SPh, O*t*-Bu, SMe, OMe, Me; R_2 = H, Me, SMe Yield = 0-99%

Improved synthesis of 1,4-phenanthrenequinones from Diels–Alder cycloadditions of 2-(*p*-tolylsulfinyl)-1,4-benzoquinone [72]



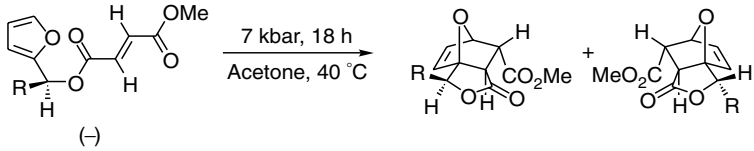
9 examples Yield = 19-80%

Regiocontrolled and stereocontrolled Diels–Alder cycloadditions of 2-pyrones and unactivated unbranched 1-alkenes [73]



R = *n*-Pr, $CH_2Si(OEt)_3$, CH_2CH_2OSBT, CH_2CH_2OBn, CH_2OSBT; R_1 = Br, CO_2Me Yield 64-80%

High-pressure and thermally induced intramolecular Diels–Alder reactions of furfuryl fumarates. Influence of tether substituents on diastereoselectivity [74]



R = Me, Et, *i*-Pr, *t*-Bu, *neo*-Pn, Ph Yield = 36-96% d.e. = 10-86%

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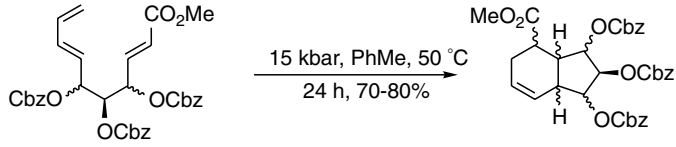
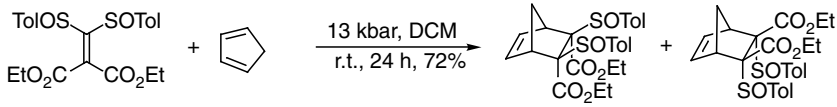
Intramolecular Diels–Alder reaction of chiral highly oxygenated trienoates derived from sugar allyltins [75]



3 examples

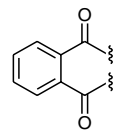
(S,S)-1,1-Bis-ethoxycarbonyl-2,2-bis-*p*-tolylsulfinyl ethene: a highly diastereoselective but unexpectedly unreactive dienophile in asymmetric Diels–Alder reactions [76]



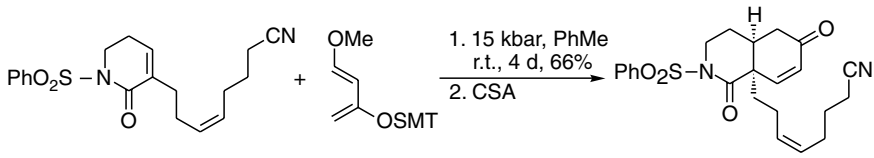
(S,S) (+) 87% 13%

4 examples Yield = 10-82%

Intermolecular *hetero*-Diels–Alder reactions of enamino ketones with highly substituted vinyl ethers. Effect of high pressure on the kinetics and diastereoselectivity [77]

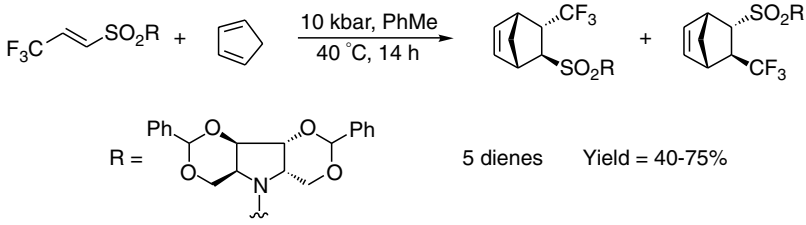
X = F, Cl Pht =  5 examples Yield = 48-95%

Diels–Alder reaction of the dihydropyridinones. V: Approach to the ircinal B core [78]

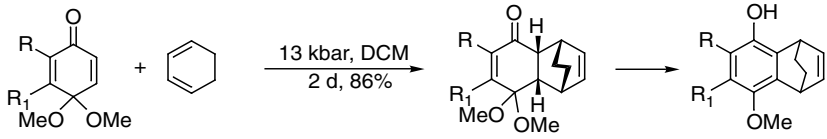


66 %

Facile synthesis of optically active trifluoromethylated compounds: asymmetric Diels–Alder reaction of trifluoromethylated α,β-unsaturated sulfonamide under high-pressure conditions [79]



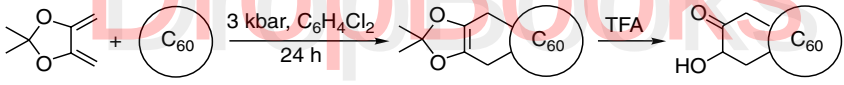
The high pressure Diels–Alder reactions of quinone-mono-ketals [80]



R = Et, R_1 = H ; R = H, R_1 = Me Yield = 31-96%

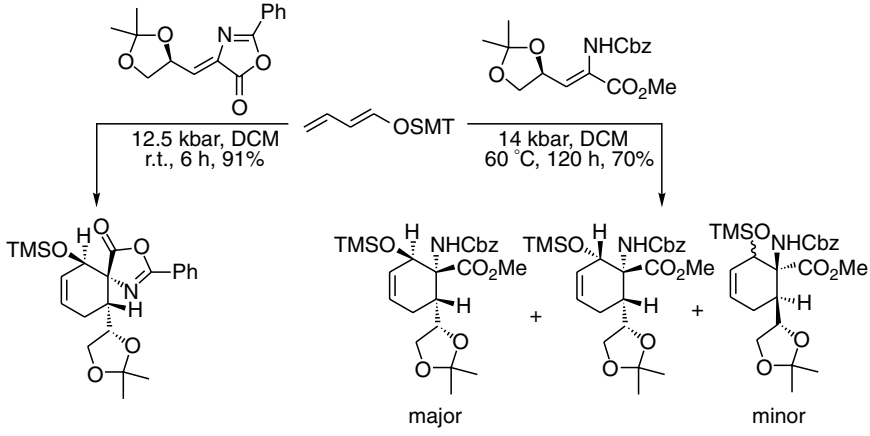
Exohedral functionalization of [60]-fullerene by [4+2] cycloadditions. Diels–Alder reactions of [60]-fullerene with electron-rich 2,3-dioxy-substituted-1,3-butadienes [81]

DropBooks

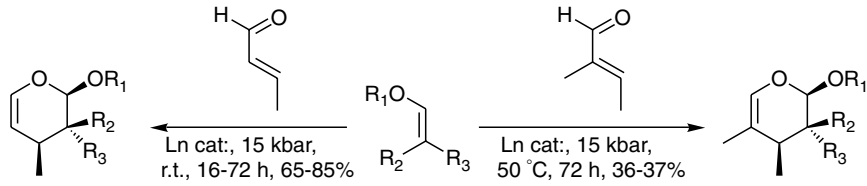


33% overall yield

High-pressure and thermally induced asymmetric Diels–Alder cycloadditions of heterosubstituted dienes to homochiral α,β-didehydro amino acid derivatives [82]



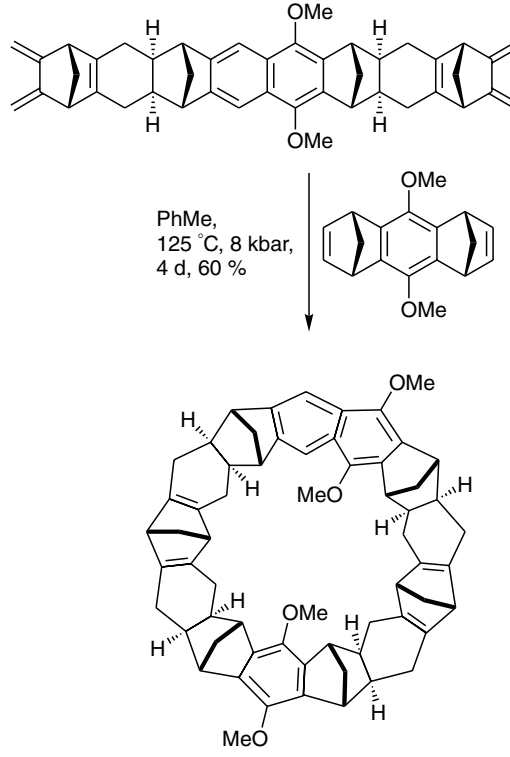
Synthesis of highly functionalized 3,4-dihydro-2H-pyrans by high-pressure Lewis-acid-catalyzed cycloaddition of enol ethers and α,β-unsaturated aldehydes [83]



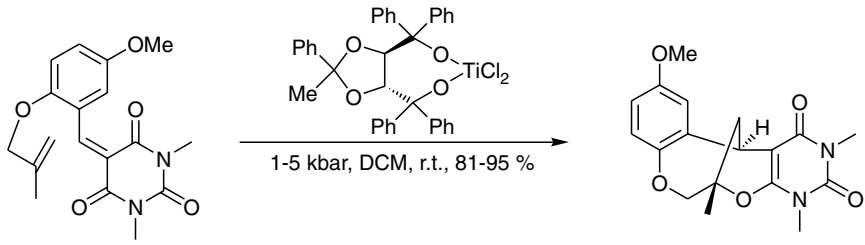
R_1 = *i*-Pr, R_2 = Me, R_3 = H

R_1 = Et, R_2 = Me, R_3 = Me

Synthesis of sterically rigid macrocycles by the use of pressure-induced repetitive Diels–Alder reactions [84]

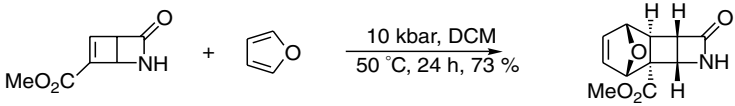


The first example of an increase in the enantioselectivity of a chemical reaction in the presence of a chiral Lewis acid under high pressure [85]



ee = 4.5 (1 bar)
ee = 20.4 (5 kbar)

Synthesis and high-pressure Diels–Alder cycloadditions of 6-methoxycarbonyl-3-oxo-2-azabicyclo[2.2.0]hex-5-ene [86]



4 dienes

Yield: 70-88 %

High-pressure organic chemistry. Part 17. Diels–Alder reaction of methyl palustrate with maleic anhydride and N-phenylmaleimide [87]

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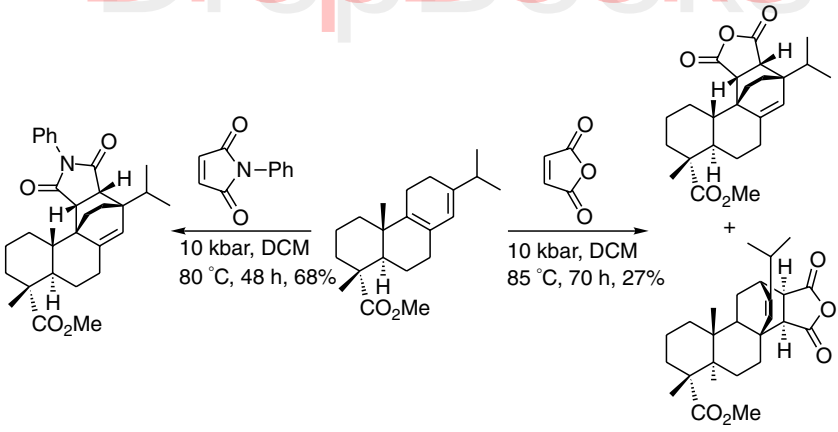
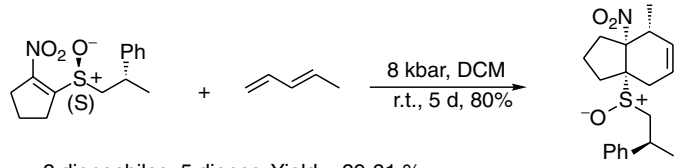
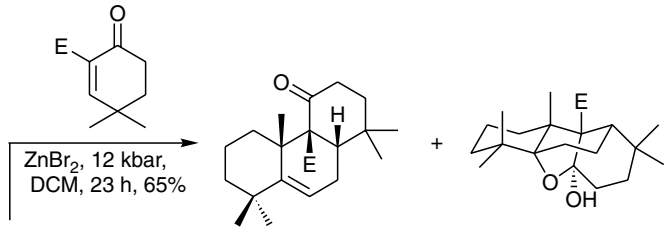


Diastereoselective Diels–Alder reactions with chiral sulfinyl derivatives as dienophiles under high pressure [88]

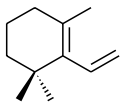


3 dienophiles, 5 dienes, Yield = 39-81 %

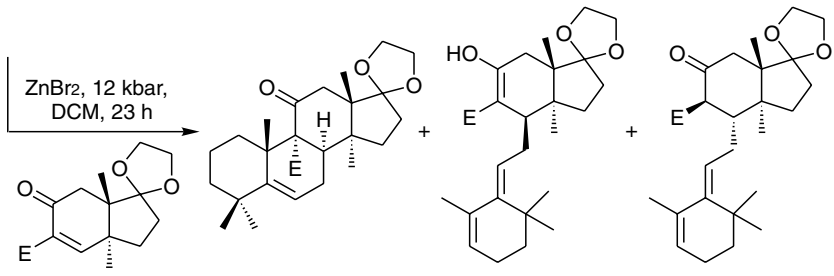
Studies on Diels–Alder reactions of 1,3,3-trimethyl-2-vinylcyclohexene with 2-cyclohexenones [89]



major

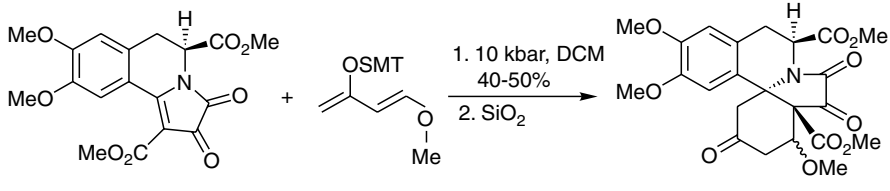


E = CO_2Me

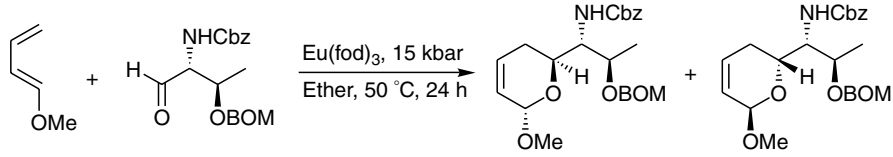


major

Total synthesis of (+)-erysotrine via asymmetric Diels–Alder reaction under super high pressure [90]

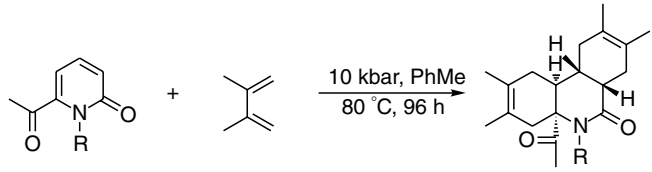


High-pressure [4 + 2] cycloaddition of 1-methoxy-1,3-butadiene to *N,O*-protected D-threoninals and D-allo-threoninals [91]



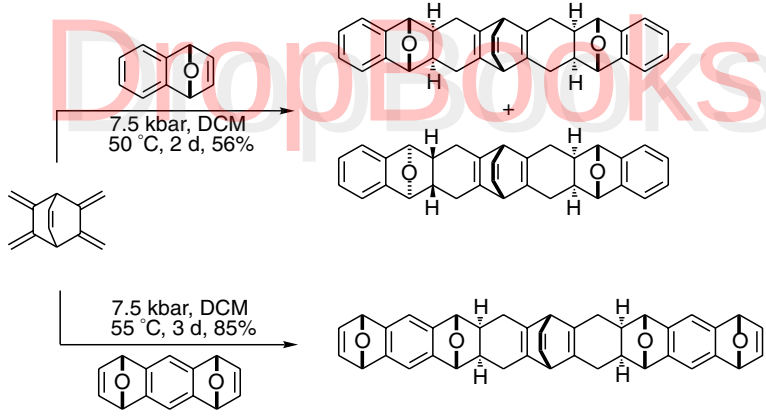
4 dienophiles

Double Diels–Alder cycloadditions of 2-(1H)-pyridones acting as dienophiles [92]

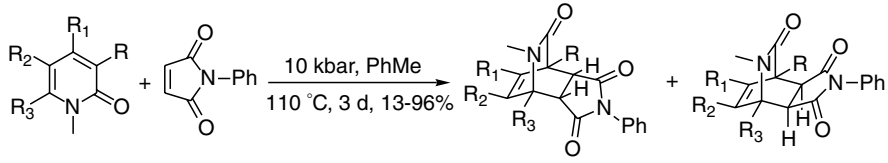


R = H, Me Yield = 11-19%

5,6,7,8-Tetramethylenebicyclo[2.2.2]oct-2-ene as 'bisdiene' in repetitive Diels–Alder reactions [93]



High-pressure Diels–Alder reaction of 1-methyl-2-(1H)-pyridones having a phenyl group with N-phenylmaleimide [94]



R = R_1 = R_2 = R_3 = H, Ph *endo/exo* = 0.5–9.5

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6 Diels–Alder Reaction in Unconventional Reaction Media

The idea that the reaction medium is a passive medium in which the dissolved material simply diffuses has been abandoned and chemists now realize that the reaction medium can greatly influence both the reactivity and selectivity of a process [1].

The choice of reaction medium is important and the most important criteria that must be complied with are (i) unreactivity towards reactants and products, (ii) a large range between the melting and boiling points, (iii) good chemical and thermal stability, (iv) compatibility with the analytical methods used to test the reaction, and (v) good solubility of the reactants, and sometimes of products, even if excellent results can be obtained in the heterogeneous phase.

Additional parameters must be considered for a reaction medium used for industrial purposes, such as price, explosiveness, inflammability, viscosity, toxicity, corrosiveness and recyclability.

Organic solvents have been the commonly used reaction medium in organic reactions, but during the last 20 years (in part stimulated by problems connected with environmentally sustainable growth) new reaction media have emerged which have given surprising and exceptional results. Water, lithium salts in diethyl ether and nitromethane, ethylene glycol, phenols, ionic liquids, microemulsions and supercritical fluids are those that have given the best results.

6.1 DIELS–ALDER REACTION IN AQUEOUS MEDIUM

In 1980, organic chemists recognized the potential of the aqueous medium as a reaction medium when Breslow [2] showed that some Diels–Alder reactions were strongly accelerated when carried out in water in comparison with the same reactions performed in organic solvent.

Interest in the aqueous medium spread quickly and many, sometimes surprising, discoveries were made [3]. Today pericyclic [4], condensation [5], oxidation [6] and reduction [7] reactions are routinely carried out in aqueous medium. The recent discovery of water-tolerant Lewis acids such as lanthanide triflates, $Bi(OTf)_3$, $Sc(OTf)_3$ and $Y(OTf)_3$ has revolutionized organometallic chemistry [5a, 7].

The aqueous medium offers notable advantages with respect to organic solvents: (i) it is abundant, cheap, non-toxic and environmentally friendly, (ii)

inflammable solvents are not handled, (iii) the reaction products can sometimes be isolated simply by decantation or filtration, (iv) the protection–deprotection of certain functional groups (OH, COOH) may be unnecessary, (v) water-soluble compounds can be used directly without derivatization, (vi) salts, surfactants and cyclodextrins can be used, and (vii) the pH can be carefully controlled, which allows the reactivity and selectivity of the reaction to be strongly influenced [8].

Aqueous medium does not mean water only but also includes homogeneous mixtures of water and organic solvents (mainly THF, EtOH, MeOH and MeCN). The reaction can be carried out in either the homogeneous or the heterogeneous phase. The use of cosolvents and salting-in agents (guanidinium chloride, $LiClO_4$) allows the reaction to occur in the homogeneous phase but this may not favor the reactivity and selectivity of the process.

Water has physical–chemical properties that are very different from those of other solvents [1] and its role in enhancing the reactivity and selectivity of some organic reactions is still a debated question. Recent experimental studies [3e, 9] and computer simulations [10] seem to indicate, at least with respect to the rate enhancement of aqueous Diels–Alder reactions, that the main effects are due to the enforced hydrophobic interactions and hydrogen bond interactions.

Among the organic reactions that have been investigated in aqueous medium, the Diels–Alder cycloaddition has been the most studied owing to its great importance from the synthetic and theoretical point of view [7a, b]. In this section Diels–Alder reactions carried out in water under conventional conditions of temperature and pressure will be illustrated. The use of water at supercritical or near-supercritical conditions will be discussed in Section 6.4.

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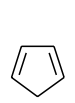
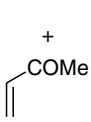
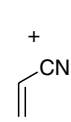
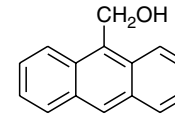
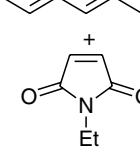
6.1.1 Uncatalyzed Diels–Alder Reaction

The cycloaddition between furan and maleic anhydride was the first uncatalyzed aqueous Diels–Alder reaction reported in the literature and was studied by Diels and Alder themselves [11]. This cycloaddition was successfully revised by Woodward and Baer [12] and some years later by De Koning and coworkers [13]. The aqueous medium was also used in the cycloaddition of aromatic diazonium salts with methylsubstituted 1,3-butadienes [14].

Rideout and Breslow first reported [2a] the kinetic data for the accelerating effect of water, for the Diels–Alder reactions of cyclopentadiene with methyl vinyl ketone and acrylonitrile and the cycloaddition of anthracene-9-carbinol with N-ethylmaleimide, giving impetus to research in this area (Table 6.1). The reaction in water is 28 to 740 times faster than in the apolar hydrocarbon isooctane. By adding lithium chloride (salting-out agent) the reaction rate increases 2.5 times further, while the presence of guanidinium chloride decreases it. The authors suggested that this exceptional effect of water is the result of a combination of two factors: the polarity of the medium and the

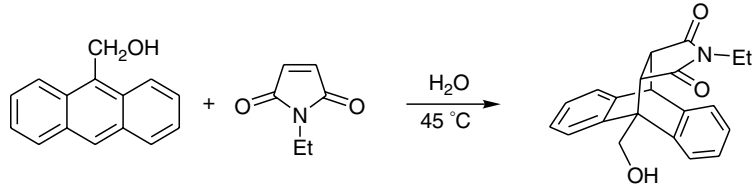
Table 6.1 Relative reaction rates of Diels–Alder reactions in water and organic solvents ($k_{rel} = k_{solvent}/k_{isooctane}$)

	Reactants		
	 + 	+ 	 + 
Reaction temperature and medium	k_{rel}	k_{rel}	k_{rel}
T (°C)	20	20	45
Isooctane	1	1	1
Methanol	13	2	0.43
Water	740	31	28

hydrophobic interaction, namely the entropy-favored association of apolar groups or apolar molecules in water (hydrophobic packing of diene and dienophile). The effects of lithium chloride and guanidinium chloride support the idea of hydrophobic packing. The presence of lithium chloride increases the reaction rate because the salt makes the apolar reactants less soluble in water and in so doing it enhances the hydrophobic interaction. The guanidinium chloride has the opposite effect because the salt increases the solubility of apolar reagents in water, which decreases the hydrophobic interaction. The salt effect is also related to the ionic radius of the anion [15a]. Thus, the rate of the aqueous Diels–Alder reaction of anthracene-9-carbinol and N-ethylmaleimide decreases as the radius of the sodium salt anion increases and as the size of the guanidinium salt anion increases (Table 6.2). The internal pressure (a change in internal energy of water as a consequence of the very small thermal expansion), as altered by the salt, has also been suggested [15b] to be an important parameter in explaining the effect of salt in aqueous Diels–Alder reactions.

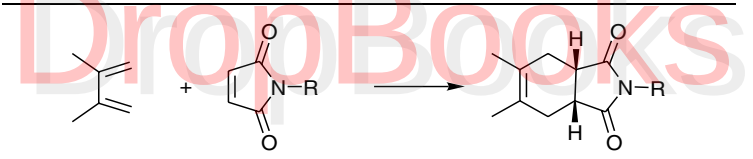
Engberts [3e, 9] has extensively investigated the Diels–Alder reaction in aqueous medium. Recently Engberts and colleagues reported [9c] a kinetic study of a Diels–Alder reaction of N-alkyl maleimides with cyclopentadiene, 2,3-dimethyl-1,3-butadiene and 1,3-cyclohexadiene in different solvents. The reaction rates of the cycloadditions with the open-chain diene relative to *n*-hexane are reported in Table 6.3. The aqueous medium greatly accelerates the Diels–Alder reaction and the acceleration increases as the hydrophobic character of the alkyl group of the dienophile increases. These and other kinetic data [3e, 9], along with the observation that the intramolecular Diels–Alder reaction is also accelerated in

Table 6.2 Sodium and guanidinium salt effects (relative reaction rates) of Diels–Alder reaction of anthracene-9-carbinol and N-ethylmaleimide



$X^{\ominus}$	NaX (k_{rel})	$C(NH_2)_3X$(k_{rel})	Ionic radii (Å)
None	1.00	1.00	—
Cl	1.34	0.56	1.67
Br	1.30	0.50	1.82
BF_4	0.98	0.40	2.44
SCN	—	0.38	—
ClO_4	0.89	0.37	2.64
PF_6	0.83	—	2.81
AsF_6	0.78	—	2.89

Table 6.3 Relative reaction rates of Diels–Alder reactions between 2,3-dimethyl-1,3-butadiene and N-alkylmaleimides in different solvents at 25 °C ($k_{solvent}/k_{n\text{-hexane}}$)



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		k_{rel}			
Solvent	R =	Me	Et	Pr	Bu
C_6H_{14}		1	1	1	1
MeCN		2.4	2.4	2.3	2.0
EtOH		7.3	7.0	6.9	6.1
PrOH		8.7	8.0	8.4	8.8
TFE		81	76	77	80
H_2O		1000	1447	1683	1881

aqueous medium, have led to the proposal that the major factor that contributes to the rate enhancement of the Diels–Alder reaction in water is the enforced hydrophobic interactions and not the hydrophobic packing of the reactants. The term 'enforced hydrophobic interactions' is used to emphasize that the hydrophobic interactions are an integral part of the activation process and contribute to stabilize the transition state relative to the initial state. A moderate acceleration can also be noted (Table 6.3) when the reaction is performed in

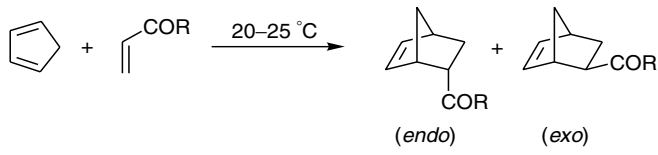
1,1,1-trifluoroethanol (TFE), a solvent with a strong hydrogen-bond donor capacity. This supports the idea that hydrogen-bonding interactions also contribute noticeably to the acceleration of aqueous Diels–Alder reactions.

The aqueous medium also has beneficial effects on the diastereoselectivity of the Diels–Alder reactions. The *endo* addition that occurs in the classical cycloadditions of cyclopentadiene with methyl vinyl ketone and methyl acrylate is more favored when the reaction is carried out in aqueous medium than when it is performed in organic solvents (Table 6.4) [2b, c].

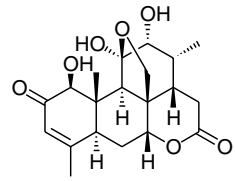
The synthesis of chaparrinone and other quassinoids (naturally occurring substances with antileukemic activity) is another striking example [16a–c]. The key step of synthesis was the Diels–Alder reaction between the α,β-unsaturated ketoaldehyde **1** (Scheme 6.1) with ethyl 4-methyl-3,5-hexadienoate **2** (R = Et). In benzene, the *exo* adduct is prevalent but it does not have the desired stereochemistry at C-14. In water, the reaction rate nearly doubles and both the reaction yield and the *endo* adduct increase considerably. By using the diene acid **2** (R = H) the reaction in water is 10 times faster than in organic solvent and the diastereoselectivity and the yield are satisfactory. The best result was obtained with diene sodium carboxylate **2** (R = Na): when the reaction is conducted 2M in diene the reaction is complete in 5 h and the *endo* adduct is 75% of the diastereoisomeric reaction mixture.

The study was extended to other dienes and dienophiles [16d, e]. Some examples and comparisons are reported in Scheme 6.2. With respect to the organic solvent, the aqueous reaction requires milder conditions and the reactionis faster and more selective. It is significant that the use of cosolvents such as methanol, dioxane and tetrahydrofuran results in a reduction of reaction rate.

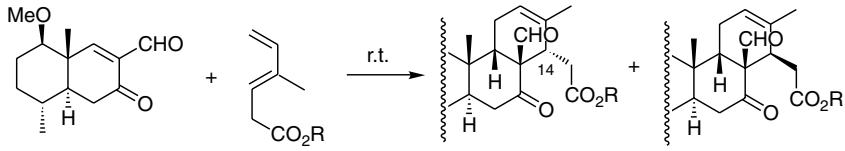
Table 6.4 *Endo*/*exo* diastereoselectivity of Diels–Alder reactions in water and organic media



	Endo / Exo	
Medium	R = OMe	R = Me
None (excess of diene)	74:26	79:21
Isooctane	69:31	
Ethanol	84:16	89:11
1-Butanol	83:17	
Formamide	87:13	
N-Methylacetamide	82:18	
Water	90:10	96:14



Chaparrinone



1 **2** (*endo*) (*exo*)

R	Medium	t(h)	endo/exo	Yield (%)
Et	PhH	288	46:54	52
Et	H_2O	168	56:44	82
H	PhMe	168	41:59	46
H	H_2O	17	60:40	85
Na	H_2O	5	75:25	100

Scheme 6.1

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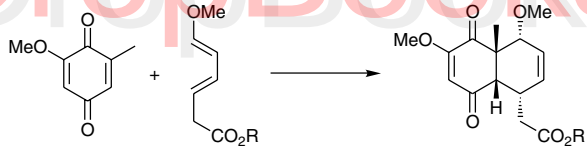
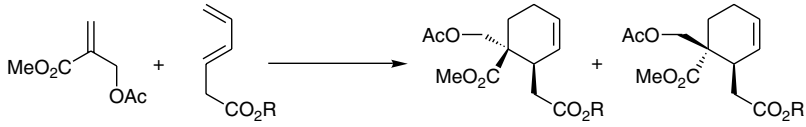


R	Medium	t(min)	T(°C)	Yield(%)
Me	PhH	720	80	69
Na	H_2O	12	r.t.	93

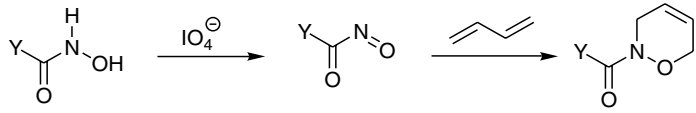


R	Medium	t(h)	*T*(°C)	(*endo*) *endo/exo*	(*exo*) yield(%)
Me	PhMe	96	110	33:66	84
Na	H_2O	24	60	67:33	67

Scheme 6.2

The nitroso moiety of the N-acylnitroso function is a powerful dienophile and therefore N-acylnitroso compounds are trapped rapidly, especially in an intramolecular reaction, with a diene allowing the Diels–Alder reaction to occur also in water, although N-acylnitroso compounds are short-lived in aqueous medium.

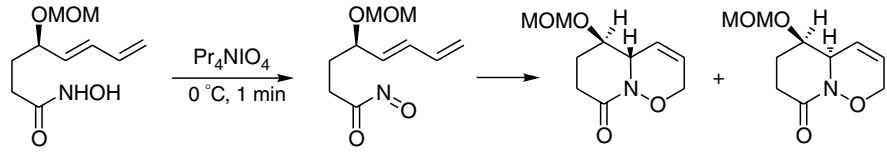
N-Acylnitroso compounds **4** are generated *in situ* by periodate oxidation of hydroxamic acids **3** and react with 1,3-dienes (e.g. butadiene) to give 1,2-oxazines **5** (Scheme 6.3). The periodate oxidation of 4-O-protected homochiral hydroxamic acid **6** occurs in water in heterogeneous phase at 0 °C, and the N-acylnitroso compound **7** that is generated immediately cyclizes to *cis* and *trans*-1,2-oxazinolactams (Scheme 6.4) [17a, b]. When the cycloaddition is carried out in $CHCl_3$ solution, the reaction is poorly diastereoselective. In water, a considerable enhancement in favor of the *trans* adduct is observed.



3 **4** **5**

Y = R, OR, NR_1R_2

Scheme 6.3



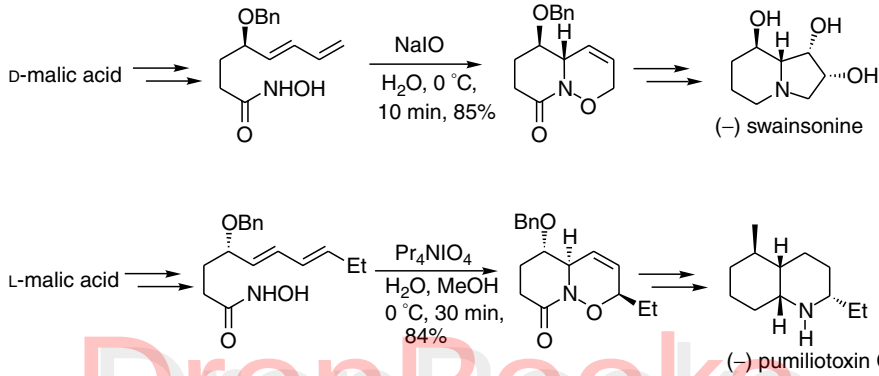
6 **7** *(trans)* *(cis)*

Medium	*trans/cis*	Yield (%)
$CHCl_3$	63:37	75
H_2O	82:18	93

Scheme 6.4

The acylnitroso approach has been used for the enantioselective syntheses of (−)-swainsonine and (−)-pumiliotoxin C [17d] (Scheme 6.5).

Lubineau and coworkers [18] have shown that glyoxal **8** ($R_1 = R_2 = H$), glyoxylic acid **8** ($R_1 = H$, $R_2 = OH$), pyruvic acid **8** ($R_1 = Me$, $R_2 = OH$) and pyruvaldehyde **8** ($R_1 = H$, $R_2 = Me$) give Diels–Alder reactions in water with poor reactive dienes, although these dienophiles are, for the most part, in the hydrated form. Scheme 6.6 illustrates the reactions with (E)-1,3-dimethyl-butadiene. The reaction yields are generally good and the ratio of adducts **9** and **10** reflects the thermodynamic control of the reaction. In organic solvent, the reaction is kinetically controlled and the diastereoselectivity is reversed.



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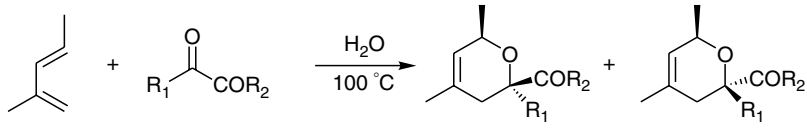
Scheme 6.5



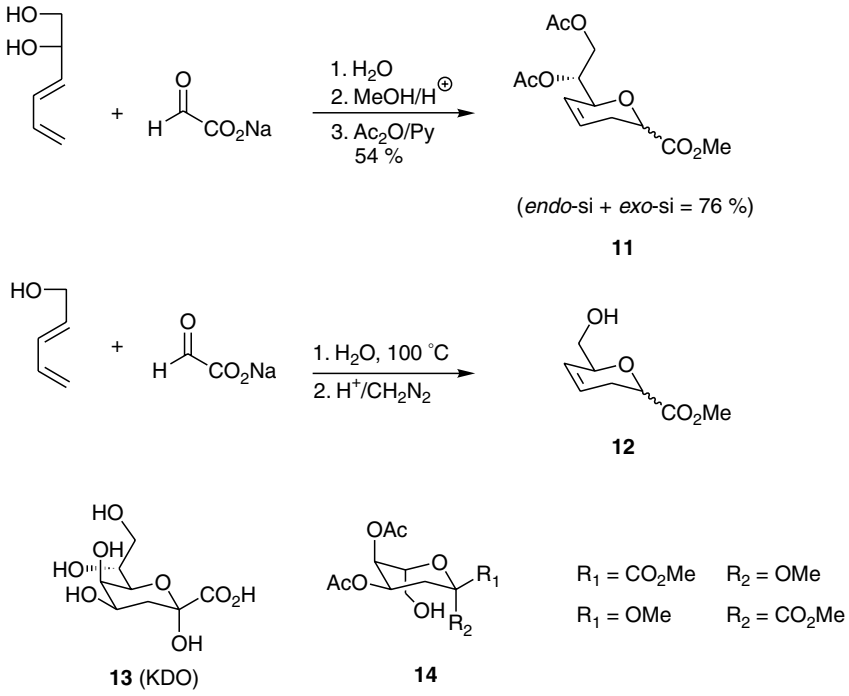
8 **9** **10**

R_1	R_2	*t* (h)	**9/10**	Yield (%)
H	OH	1.5	64:36	97
H	Me	48	53:47	96
H	H	60	50:50	36
Me	OH	48	33:67	74

Scheme 6.6

These results have been used to prepare key starting compounds **11** and **12** for the enantioselective synthesis of 3-deoxy-D-manno-2-octulosonic acid

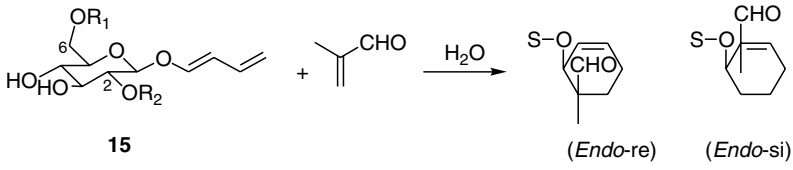
(KDO) **13** [19a] and for a concise synthesis of ketodeoxyheptulosonic acid derivatives **14** [19b], respectively (Scheme 6.7).

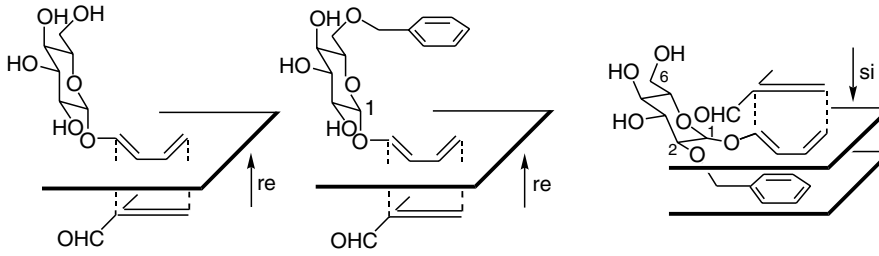


Scheme 6.7

Extensive work has been done by using buta-1,3-dienyl-glycosides of unprotected sugar to study aqueous Diels–Alder reactions and to prepare optically active oligosaccharides [20].

The cycloaddition of β-glucoside **15** ($R_1 = R_2 = H$) (Scheme 6.8) with methacrolein in water leads to a mixture of two *endo* adducts, the majority of which results from an approach of the dienophile part of glucoside to the *re* face of the diene as depicted in **16**. A benzyl protecting group at O-6 (**15**; $R_1 = Bn$, $R_2 = H$) slows the reaction rate but does not influence the *endo/exo* diastereoselectivity or the face selectivity of the reaction (Scheme 6.8; **17**). A reversal face selectivity occurs when the protecting group is at O-2 as illustrated in **18**. The interaction between the phenyl ring and diene unit is enhanced by a hydrophobic interaction; the use of water therefore favors the packing and consequently the s*i* approach.



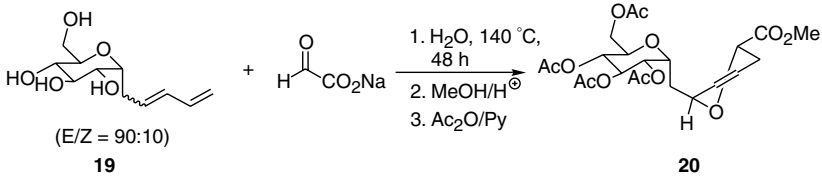


R_1	R_2	T (°C)	t (h)	re/si	*endo*/*exo*	Yield (%)
H	Et	20	3.5	60:40	100:0	90
Bn	H	40	17	69:31	95:5	86
H	Bn	40	17	34:66	93:7	95

Scheme 6.8

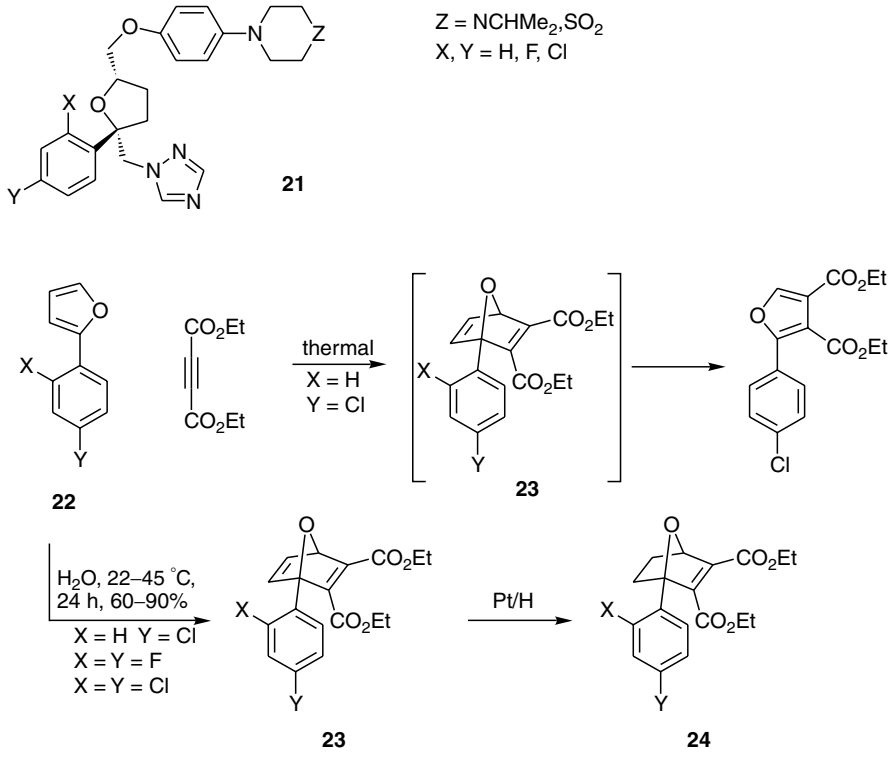
DropBooks

C-Disaccharide analogs of trehalose were recently [20c] prepared by using as a key step an aqueous Diels–Alder reaction between the sodium salt of glyoxylic acid and the water soluble homochiral glucopyranosil-1,3-pentadiene **19** (Equation 6.1). A mixture of four diastereoisomers in a 41:24:21:14 proportion was obtained after esterification with methanol and acetylation. The main diastereoisomer **20** was isolated and characterized as benzoyl-derivative.



(6.1)

Aqueous Diels–Alder reaction has also been applied at the industrial level. 2,2,5-Trisubstituted tetrahydrofurans **21** are a class of active azole antifungals. Workers at Schering-Plough [21] developed a synthetic approach based on a Diels–Alder reaction between 2-arylfurans **22** and ethyl acetylenedicarboxylate (Scheme 6.9). Under thermal conditions the reaction gave a low yield of



Scheme 6.9

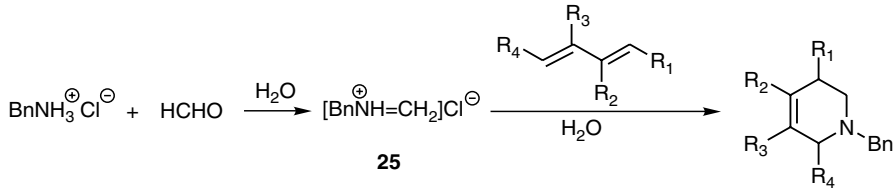
a useless product since cycloadduct **23** underwent a retro-Diels–Alder reaction. In water, the desired adducts **23** can be easily isolated in high yield and then be converted into the biologically active compounds **21** via chemoselective hydrogenation and regioselective manipulation of the dihydrofuran moiety of **24**.

6.1.2 Catalyzed Diels–Alder Reaction

Catalyzed organic reactions in water, and the aqueous Diels–Alder reactions in particular, are currently a topic of great interest [3f–h].

Simple imines are poor dienophiles and must be activated by protonation or by attaching an electron-withdrawing group to the nitrogen atom. Scheme 6.10 illustrates the Diels–Alder reactions of benzyliminium ion **25**, generated *in situ* from an aqueous solution of benzylamine hydrochloride and commercial aqueous formaldehyde, with methylsubstituted 1,3-butadienes [22]. This aqueous Diels–Alder reaction combines three components (an aldehyde, an amine

salt and a diene) and occurs under mild conditions and with satisfactory yields. The highly reactive cyclopentadiene reacts quantitatively in three hours at 25 °C [22].

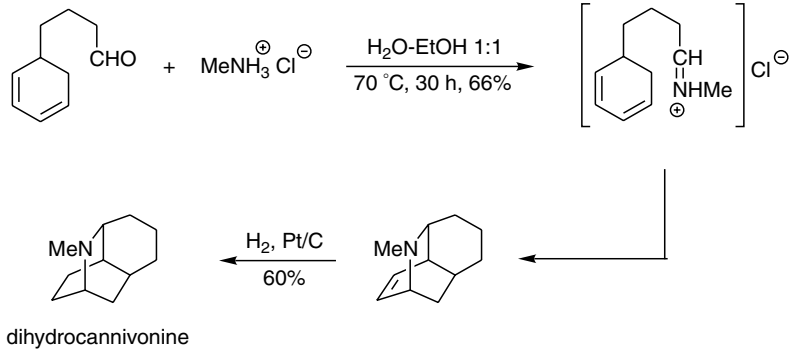


R_1	R_2	R_3	R_4	T(°C)	t (h)	Yield (%)
H	Me	H	H	35	70	59
H	Me	H	Me	25	23	45
H	Me	Me	H	35	48	64
Me	H	H	Me	55	96	62

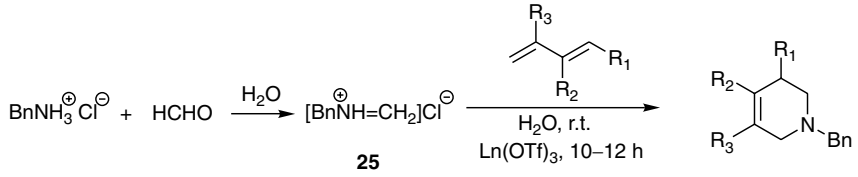
Scheme 6.10

The intramolecular version, achieved by using both dienyl amine and dienyl-aldehydes, has also been investigated and applied to the synthesis of dihydrocannivonine [23] (Scheme 6.11).

The aqueous aza-Diels–Alder reaction of an aldehyde and an amine hydrochloride with a diene is catalyzed by lanthanide(III) trifluoromethane sulfonates ($Ln(OTf)_3$, triflates [24]). Some examples are reported in Schemes 6.12 and 6.13. With respect to uncatalyzed reactions, the lanthanide catalyst allows milder reaction conditions, increases the reaction yield and does not affect the diastereoselectivity of the reaction, but influences the regiochemistry as in the cycloaddition of **25** with 1,3-dimethyl-1,3-butadiene (Schemes 6.10 and 6.12). These results have been applied [24b–d] to the synthesis of azasugars (Scheme 6.14).

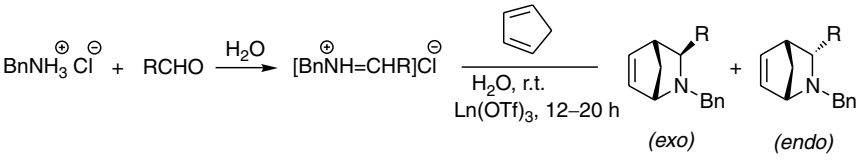


Scheme 6.11



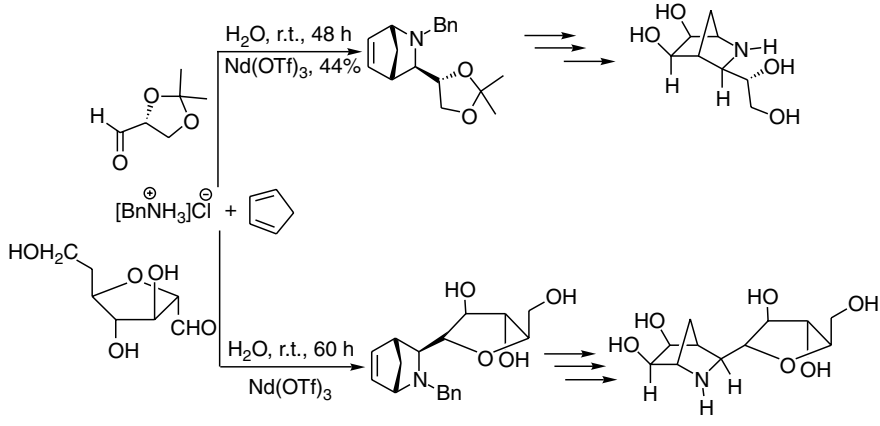
				Yield (%)	
R_1	R_2	R_3	Ln	catalyzed	uncatalyzed
H	Me	Me	Nd	93	23
Me	H	Me	Yb	92	54

Scheme 6.12



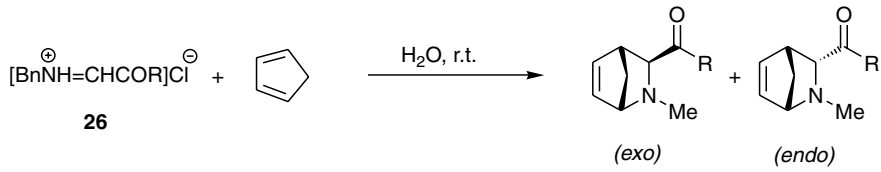
			Yield (%)	
R	Ln	*endo/exo*	catalyzed	uncatalyzed
$Me(CH_2)_4$	Pr	74:26	68	7
$Me(CH_2)_4$	Er	73:27	46	4
$Me(CH_2)_4$	Yb	72:28	62	4
Bn	Yb	80:20	72	3
Ph	Yb	99:1	7	0

Scheme 6.13



Scheme 6.14

Iminium ions bearing an electron-withdrawing group bonded to the sp^2 carbon of the iminium function are very reactive dienophiles. Thus, iminium ions **26** generated from phenylglyoxal (Scheme 6.15, R = Ph) or pyruvic aldehyde (R = Me) with methylamine hydrochloride, react with cyclopentadiene in water at room temperature with good diastereoselectivity [25] (Scheme 6.15). If glyoxylic acid is used, the formation of iminium salt requires the free amine rather than the amine hydrochloride.



R	*t*(h)	*exo/endo*	Yield (%)
Ph	22	81:19	82
Me	20	78:22	67

Scheme 6.15

Lanthanide triflates catalyze the Diels–Alder reaction of imines, generated from anilines and aldehydes, with both dienes and alkenes [26]. Thus N-benzylideneaniline in the presence of $Yb(OTf)_3$ (Scheme 6.16) reacts in organic solvent with open-chain dienes, such as Danishefsky's diene, to give tetrahydropyridine derivatives, while with cyclopentadiene and vinylethers and vinylthioethers it works like azadiene in both organic solvent and aqueous medium, affording tetrahydroquinoline derivatives.

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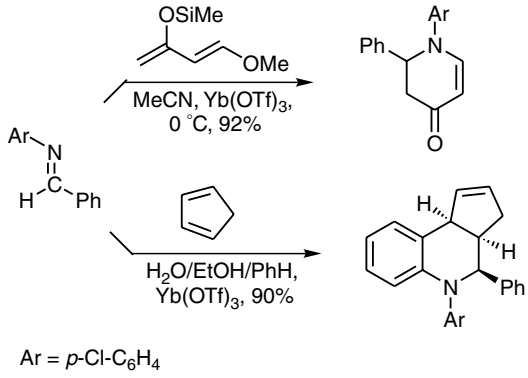
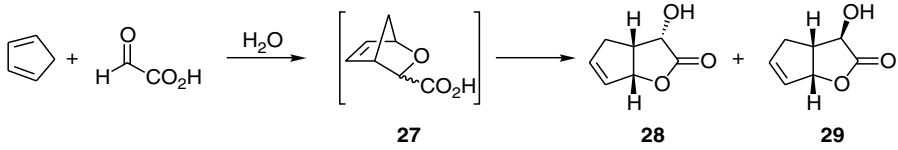
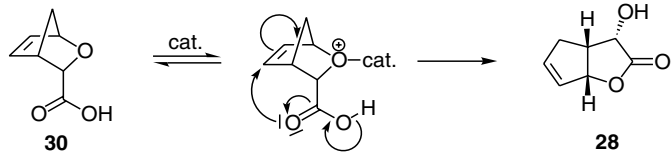


Scheme 6.16

The cycloaddition of glyoxylic acid with cyclopentadiene in water at pH 6 and 60 °C is slow and occurs with low yield and low diastereoselectivity [18] (Scheme 6.17). Proton (pH = 0.9) [18], copper salts [27] and $Bi(OTf)_3$ [28] accelerate the reaction and increase the diastereoselectivity. The lactones **28** and **29** originate from *endo* and *exo* cycloadducts **27**, respectively. The proposed rearrangement is depicted in Scheme 6.17 for the major *endo* adduct **30**. A competitive ene reaction that originates **28** and **29** cannot be excluded [28].



catalyst	*t*(h)	*T*(°C)	**28/29**	Yield(%)
pH=6	24	60	60:40	16
pH=0.9	1.5	40	73:27	83
Cu^{2+}	3	60	65:35	63
$Bi(OTf)_3$	2	40	82:18	86

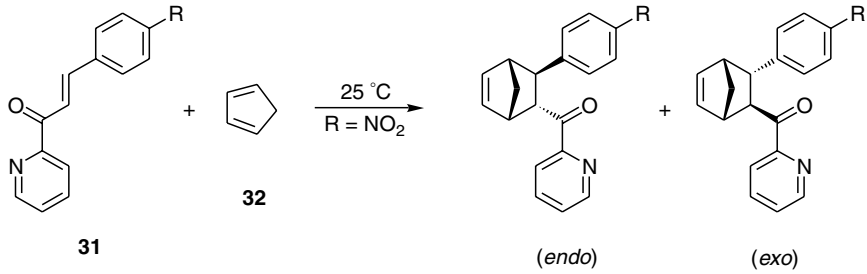


Scheme 6.17

Engberts [3e, f, 9, 29] investigated the influence of metal ions (Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}) on the reaction rate and diastereoselectivity of Diels–Alder reaction of dienophile **31** (Table 6.5, R = NO_2) with cyclopentadiene **(32)** in water and organic solvents. Relative reaction rates in different media and the catalytic effect of Cu^{2+} are reported in Table 6.5. 10^{-2}M $Cu(NO_3)_2$ accelerates the reaction in water by 808 times, and when compared with the uncatalyzed reaction in MeCN by a factor of 232 000.

Cu^{2+} is the best catalyst and, for the reaction of **31** (R = H) with cyclopentadiene (**32**), it is 25 times more active than Ni^{2+} and 55 times more active than Co^{2+} or Zn^{2+}.

Table 6.5 Relative reaction rates of Diels–Alder reaction of **31** (R = NO_2) with **32** in different media and catalytic effect[a] of Cu^{2+} ion



31 **32** (*endo*) (*exo*)

Medium	k_{rel}	Catalytic effect[a]
MeCN	1	
EtOH	2.7	
H_2O	287	
CF_3CH_2OH	482	
10^{-2} M HCl in H_2O	5442	19
10^{-2}M $Cu(NO_3)_2$ in EtOH	58 357	21 576
10^{-2}M $Cu(NO_3)_2$ in MeCN	158 000	158 000
10^{-2}M $Cu(NO_3)_2$ in H_2O	232 000	808

[a] Relative rate between the catalyzed and uncatalyzed reaction in the same solvent.

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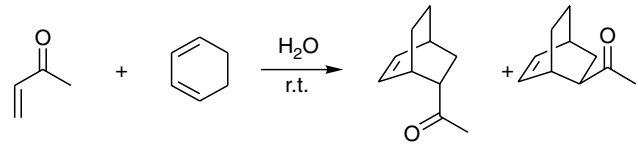
The complex obtained from commercially available chiral α-amino acids (AA) with Cu^{2+} ion induces asymmetry in the Diels–Alder reaction of **31** (R = H) with **32**. By using 10% Cu(II)-AA (AA = L-abrine) the cycloaddition occurs *endo*-stereoselectively in 48 h at 0 °C with high yield and with acceptable enantioselectivity (*ee* = 74%). This is the first example of enantioselective Lewis-acid catalysis of an organic reaction in water [9b].

Indium trichloride [30] and methylrhenium trioxide [31] catalyze the aqueous Diels–Alder reaction of acrolein and acrylates with cyclic and open-chain dienes. Some examples of the cycloaddition of methyl vinyl ketone with 1,3-cyclohexadiene are reported in Scheme 6.18. $MeReO_3$ does not give satisfactory yields for acroleins and methyl vinyl ketones with substituents at the β-position and favors the self-Diels–Alder reaction of diene.

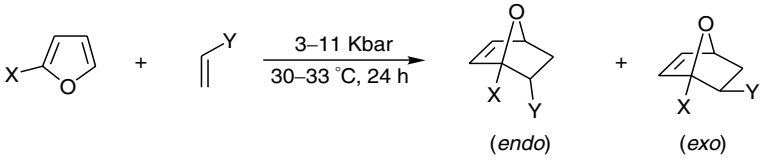


catalyst	*t* (h)	*endo*/*exo*	Yield (%)
$InCl_3$	4	90:10	87
$MeReO_3$	16	99:1	91

Scheme 6.18

The Diels–Alder reaction can be greatly enhanced by high pressure (Chapter 5) but the effect of pressure is generally weaker in aqueous medium than in organic solvent. Results of high pressure-mediated Diels–Alder reactions of furans and acrylates in water and dichloromethane are reported in Table 6.6 [32]. In aqueous medium the cycloadditions occur with lower yields and less diastereoselectivity than in dichloromethane and, in some cases, addition–substitution reactions were observed.

Table 6.6 Diels–Alder reactions of furans with acrylates in water and dichloromethane under high pressure



(*endo*) (*exo*)

Medium	X	Y	*endo*/*exo*[a]	ϑ[b]
H_2O	H	COMe	62:38	3.9
CH_2Cl_2	H	COMe	74:26	5.1
H_2O	H	CN	67:33	4.1
CH_2Cl_2	H	CN	67:33	4.6
H_2O	Me	CN	26:74	3.1
CH_2Cl_2	Me	CN	31:69	5.3

[a] At 3 kbar.
[b] Yield ratio at 3 vs 11 kbar.

6.2 DIELS–ALDER REACTION IN NON-AQUEOUS POLAR SYSTEMS

After the discovery of the remarkable acceleration of some Diels–Alder reactions performed in water, a number of polar non-aqueous solvents and their salty solutions were investigated as reaction medium. This revolutionized the concept that the Diels–Alder reaction is quite insensitive to the effect of the medium and emphasized that a careful choice of the solvent is crucial for the success of the reaction. The polarity of the reaction medium is an important variable which also provides some insights into the mechanism of the reaction. If the reaction rate increases by using a polar medium, this means that the transition state probably has polar character, while the absence of a solvent effect is generally related to an uncharged transition state.

In the following paragraphs the influence of some representative non-aqueous polar systems on the Diels–Alder reaction is illustrated.

6.2.1 Lithium Perchlorate–Diethyl Ether

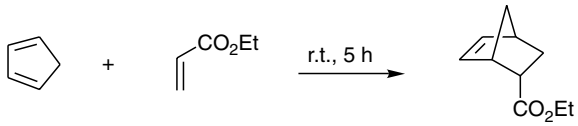
During 1989–93 lithium perchlorate–diethyl ether ($LiClO_4 - Et_2O$, LP-DE) was studied as a reaction medium in organic synthesis when it was observed that cycloadditions, sigmatropic rearrangements, Michael additions and aldol condensations carried out in LP-DE occurred quickly and selectively under mild reaction conditions [33]. In addition, LP-DE allowed the reaction and subsequent work-up to be carried out under essentially neutral conditions.

DropBooks

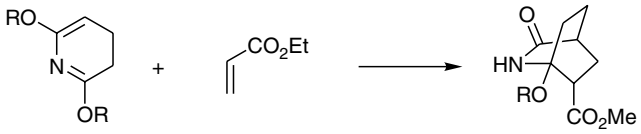
Initially the LP-DE effect was ascribed to the high internal pressure generated by the solubilization of the salt in diethyl ether [34]. Today the acceleration is explained in terms of Lewis-acid catalysis by the lithium cation [35]. The contribution of both factors (internal pressure and lithium cation catalysis) has also been invoked [36].

LP-DE has a weaker catalytic activity than $BF_3 \cdot Et_2O$, $AlCl_3$ and $TiCl_4$ because the Lewis acidity of the lithium cation is moderated by complexing with diethyl ether and perchlorate anion [37], but it becomes a highly oxophilic Lewis acid when concentrated solutions are used [38]. The concentration of LP-DE is therefore sometimes essential for the success of the reaction.

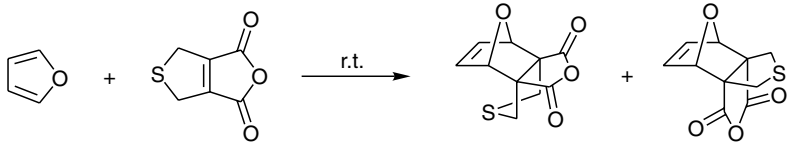
Grieco and coworkers first observed [34] that 5.0M LP-DE is an extraordinary medium for facilitating Diels–Alder reactions at room temperature. Schemes 6.19 and 6.20 illustrate some examples.



5.0M LP-DE	*endo/exo* = 89:11, yield 93%
H_2O	*endo/exo* = 80:20, yield 73%



5.0M LP-DE	r.t., 5 h, *endo/exo* = 75:25, yield 80%
PhH	60 °C, 72 h, *endo/exo* = 8:92, yield 74%



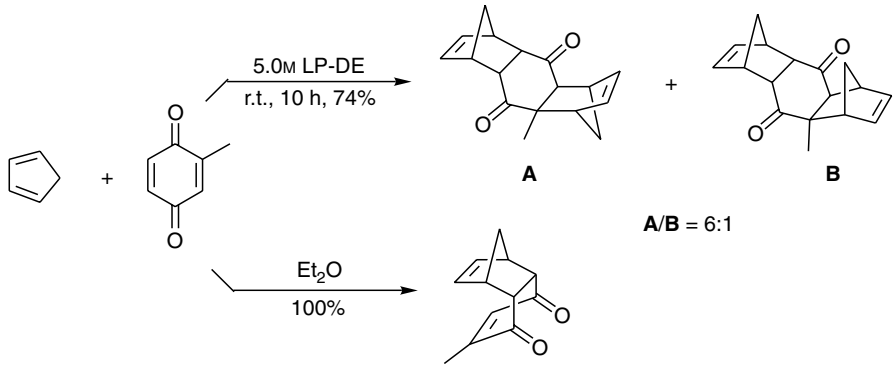
A **B**

5.0M LP-DE	9.5 h, ***A/B*** = 85:15, yield 70%
DCM	6 h, 15 kbar, **A/B** = 85:15, yield 100%

Scheme 6.19

The reaction of furan with 2,5-dihydrothiophene-3,4-dicarboxylic anhydride is remarkable (Scheme 6.19). Furan is a poor diene and requires high pressure to affect cycloadditions [39]. On the other hand, high temperatures are forbidden because cycloaddition products derived from furan undergo cycloreversion under these conditions. In 5.0M LP-DE, the Diels–Alder reaction of furan with 2,5-dihydrothiophene-3,4-dicarboxylic anhydride proceeds at room temperature and atmospheric pressure in 9.5 h with 70 % yield and with the same diastereoselectivity found when the reaction is carried out under high pressure [40].

The result of the cycloaddition of cyclopentadiene with methylbenzoquinone (Scheme 6.20) is also interesting. In 5.0M LP-DE, diasteroisomeric bis adducts are formed, while in the absence of LP-DE, only one 1:1 adduct is obtained quantitatively.



Scheme 6.20

LP-DE also promotes and accelerates intramolecular Diels–Alder reactions of low reactive polyenones. The use of a catalytic amount of camphorsulfonic acid (CSA) further accelerates the cycloaddition and enhances the diastereoselectivity [41]. Table 6.7 illustrates the effect of CSA on the intramolecular Diels–Alder reaction of 2-methyl-1,7,9-decatrien-3-one.

In contrast LP-DE gives disappointing results for intramolecular imino Diels–Alder reactions, even in the presence of CSA. This is due to the fact that weak acids become strong acids in highly polar media such as 5.0M LP-DE and the protonation of diene, with concomitant diene isomerization, competes with cycloaddition [42]. This observation was supported by using trifluoroacetic acid (TFA). The imine **33** (Scheme 6.21) in LP-DE at room temperature in the presence of TFA gave a 1:1 mixture of cycloadduct **34** and the isomerized diene **35** within the unreacted imine **33**. No Diels–Alder cycloadduct **36** was detected.

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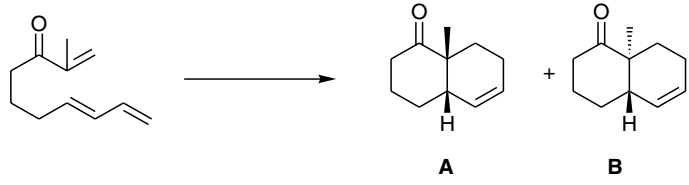
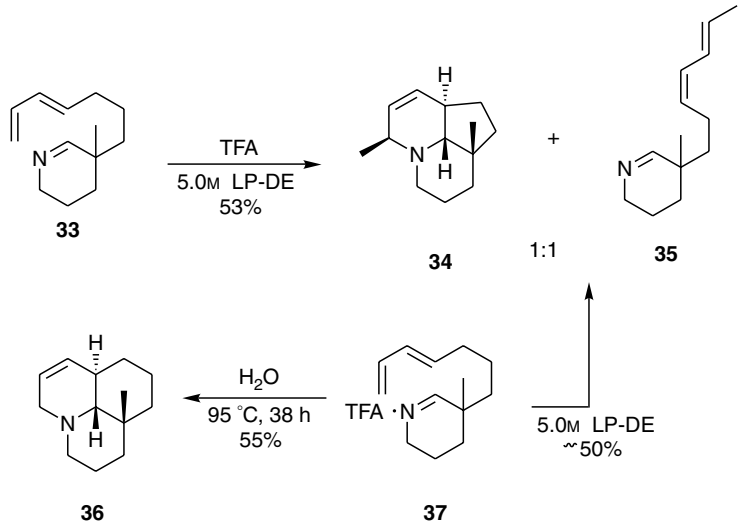
Table 6.7 Intramolecular Diels–Alder reaction of 2-methyl-1,7,9-decatrien-3-one



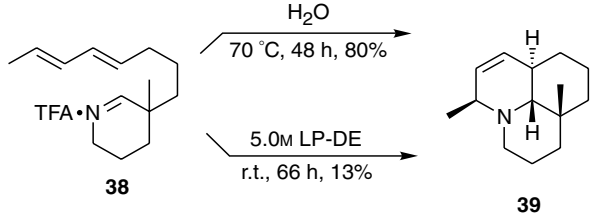
Medium	T (°C)	t(h)	A/B	Yield (%)
PhH	120	18	1.6	72
Ph, Me_2AlCl	25	3	3.0	74
5.0 M LP-DE	25	24	3.0	65
5.0 M LP-DE/CSA (1.0 mol%)	25	1.5	4.5	88
30 mol% LP-DCM	25	72	2.4	9



Scheme 6.21

Similarly, in 5.0M LP-DE, preformed TFA-iminium salt **37** gave a 1:1 mixture of **34** and **35**. In contrast, heating **37** in water alone gave the cycloadduct **36** in 55% yield.

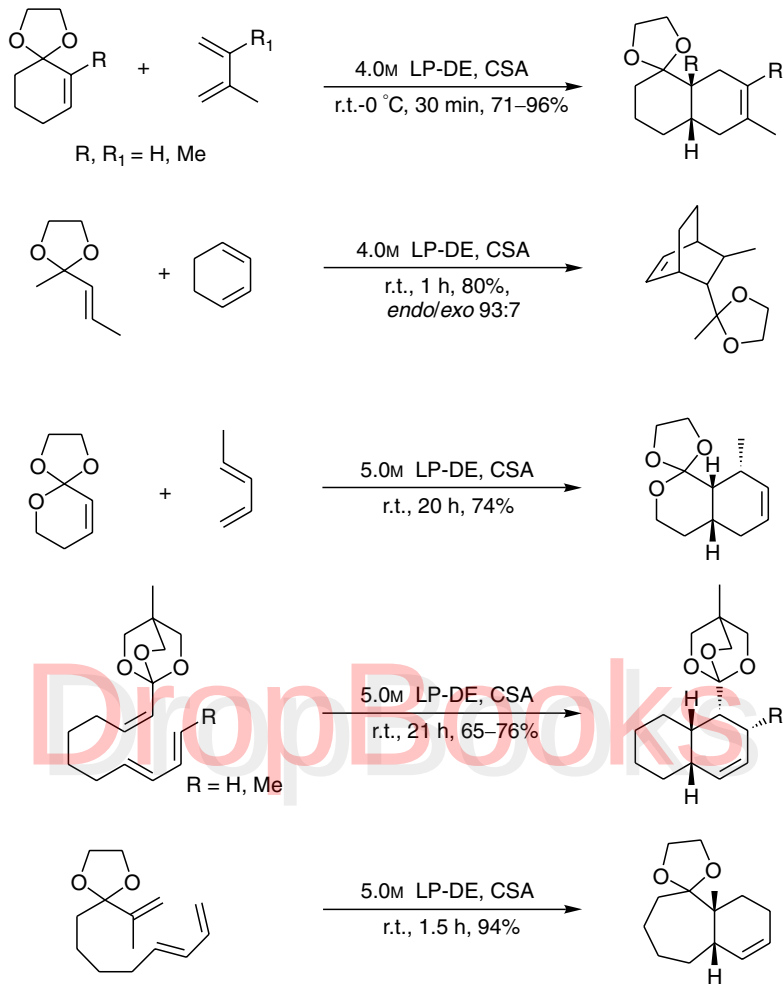
Similarly, the iminium salt **38** exposed to 5.0M LP-DE afforded only 13% of tricyclic amine **39**, while heating **38** in water gave the Diels–Alder adduct **39** in high yield (Equation 6.2).



(6.2)

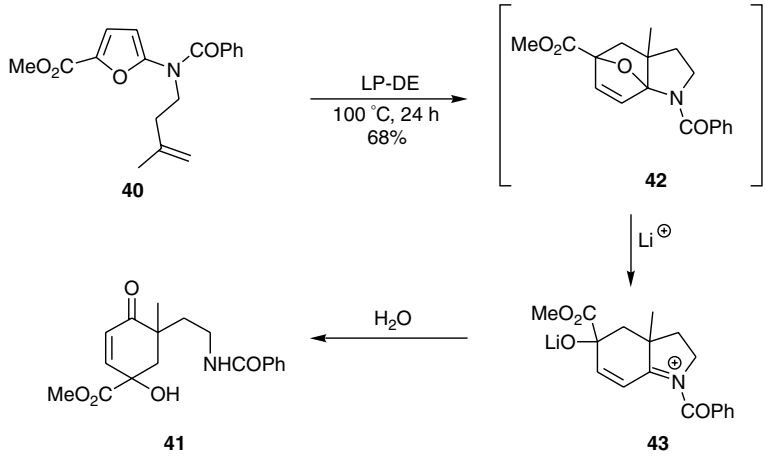
For the aza-Diels–Alder reaction illustrated above, water works better than LP-DE as a reaction medium, providing the cycloadducts in good yield with outstanding stereocontrol.

α,β-Unsaturated cycloalkenones are poor dienophiles and do not undergo Diels–Alder reaction in 5.0M LP-DE. The corresponding ketals, on the contrary, give facile cycloaddition in 4.0M LP-DE containing 1.0 mol% of CSA [43] (Scheme 6.22). Analogous results were obtained in 5.0M LP-DE, while the reaction rate was slower in 3.0M LP-DE. When CSA was used in the absence of LP-DE, no reaction occurred. The procedure has been successfully extended to ketals of acyclic α,β-unsaturated ketones, ketals of lactones and orthoesters, and intramolecular cycloaddition of ketals (Scheme 6.22) [43].



Scheme 6.22

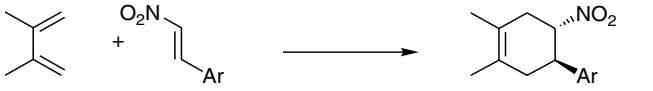
A recent example of the effectiveness of LP-DE on the Diels–Alder reaction is the intramolecular cycloaddition of 2-amidofurans containing a tethered alkenyl group during the synthesis of pyrrolophenanthridine alkaloids [44]. Furanamide **40** (Scheme 6.23) fails to undergo Diels–Alder reactions even at temperatures as high as 240 °C in toluene. The use of 4.0M LP-DE allows the cyclohexanone **41** to be isolated at 100 °C in 24 h in 68% yield. The reaction involves an initial intramolecular Diels–Alder reaction to give **42**, followed by ring opening to give the iminium **43** which then hydrolyzes to **41**.



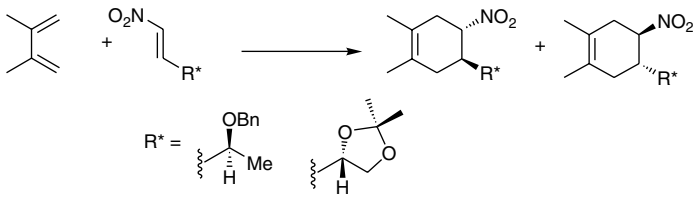
Scheme 6.23

6.2.2 Lithium Perchlorate–Nitromethane

Lithium perchlorate in nitromethane (LP-NM) is sometimes a more effective reaction medium than LP-DE for certain Diels–Alder reactions. The cycloaddition of 2,3-dimethylbutadiene with nitrostyrenes (Scheme 6.24) occurs with low



Medium	*T*(°C)	*t*(h)	conversion(%)
PhMe	115	48	22-54
5.0M LP-DE	r. t.	24	7-13
4.0M LP-NM	r. t.	67	83-86

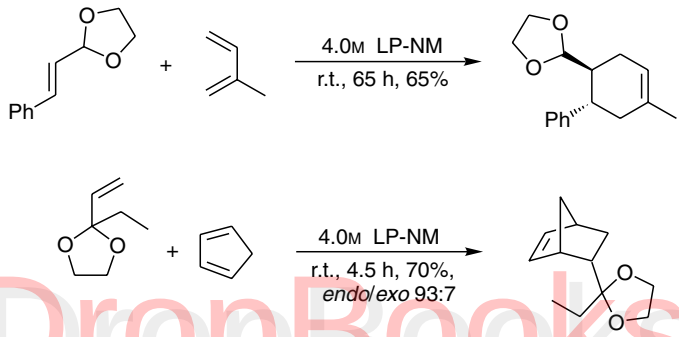


medium	*T*(°C)	*t*(h)	conversion (%)
PhMe	115	24	54-65
5.0M LP-DE	r. t.	72	60-88
4.0M LP-NM	r. t	38-96	98-100

Scheme 6.24

conversion both in toluene under reflux conditions and in 5.0M LP-DE. In 4.0M LP-NM, however, a high conversion is achieved [45]. Analogously, by using a suitable reaction time, the conversion of the Diels–Alder reaction of homochiral α,β-unsaturated nitroalchenes is quantitative in 4.0M LP-NM and the diastereoisomeric excesses are acceptable (Scheme 6.24).

The effectiveness of LP-NM with respect to LP-DE has also been proven by the cycloaddition of ketals of α,β-unsaturated ketones with open-chain and cycloaliphatic dienes [46]. In 4.0M LP-NM the Diels–Alder reaction occurs with good yields and selectivities without using CSA, which is absolutely necessary when the reaction is performed in LP-DE (Section 6.2.1). Some examples are illustrated in Scheme 6.25.



DropBooks

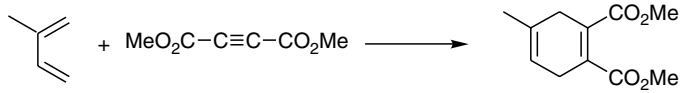
Scheme 6.25

The rate enhancement of the Diels–Alder reaction in LP-NM has been attributed to the high dipole moment of nitromethane (3.40 D) in comparison with diethyl ether (1.33 D).

6.2.3 Lithium Trifluoromethanesulfonimide in Acetone or Diethyl Ether

A convenient alternative to LP-DE is lithium trifluoromethanesulfonimide ($LiNTf_2$) in acetone or diethyl ether (LT-AC, LT-DE). Representative examples are the Diels–Alder reactions of citraconic anhydride with cyclopentadiene and of dimethyl acetylenedicarboxylate with isoprene [47] (Scheme 6.26).

Medium	T (°C)	t (h)	Yield (%)
4.0M LT-AC	r. t.	1	88
5.0M LP-DE	r. t.	1	84

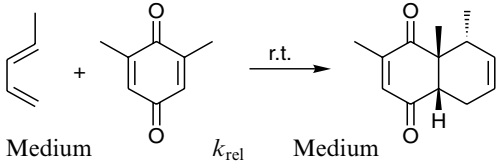


Medium	T (°C)	t (h)	Yield (%)
4.0M LT-AC	40	7	96
5.0M LP-DE	25	12	94

Scheme 6.26

Table 6.8 reports the relative reaction rates of Diels–Alder reactions of 2,5-dimethylbenzoquinone with *trans*-piperylene in different lithium salt solutions. The data show that the reaction rate depends on the concentration of LT and that in 4.0M LT-AC and 4.0M LT-DE the rate accelerations are comparable to that exhibited in 5.0M LP-DE and 5.0M LP-AC.

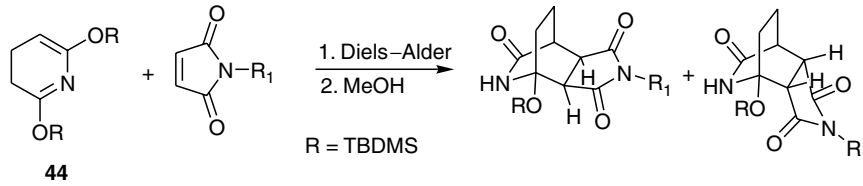
Table 6.8 Relative reaction rates of Diels–Alder reactions of 2,6-dimethylbenzoquinone with *trans*-piperylene in $LiClO_4$ (LP) and $LiNTf_2$ (LT) in acetone (AC) and diethyl ether (DE)



Medium	t (h)	Yield (%)
4.0 M LT-AC	0.5	84
4.0 M LT-DE	6	75
5.0 M LP-DE	0.5	94

Medium	k_{rel}	Medium	k_{rel}	Medium	k_{rel}
1.0 M LT-AC	1	1.0 M LP-AC	1.4	5.0 M LP-DE	265.4
2.0 M LT-AC	3.8	2.0 M LP-AC	3.4	5.0 M LP-AC	238.5
3.0 M LT-AC	65.4	3.0 M LP-AC	14.6	4.0 M LT-AC	207.7
		4.0 M LP-AC	80.8	4.0 M LT-DE	246.2

Interestingly, the cycloaddition of 2-azadiene **44** with N-methylmaleimide in 2.5M LT-DE gave predominantly *exo*-adduct in contrast to the thermal cycloaddition that is mainly *endo*-selective (Scheme 6.27). A similar but not so dramatic increase in *exo*-selectivity was also observed [47] for the cycloaddition of **44** with N-phenylmaleimide. The reaction is kinetically controlled, but the origin of the high *exo*-selectivity observed in LT-DE is unclear; the polar medium probably favors the more polar *exo* transition state.



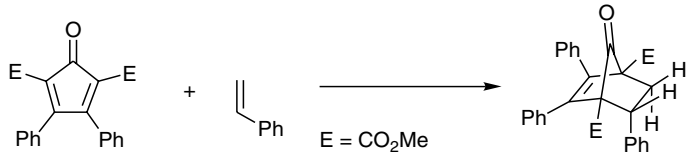
R_1	Medium	*T* (°C)	*t* (h)	*exo*/*endo*	Yield (%)
Me	PhMe	60	2	20:80	76
Me	2.5M LT-DE	r. t.	0.5	80:20	80
Ph	PhMe	r. t.	3	15:85	80
Ph	2.5M LT-DE	r. t.	0.1	55:45	96

Scheme 6.27

DropBooks

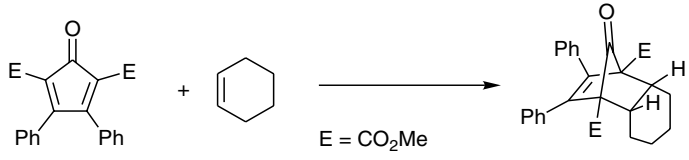
6.2.4 *para*-Chlorophenol and Ethylene Glycol

Harano and colleagues [48] found that the reactivity of the Diels–Alder reaction of cyclopentadienones with unactivated olefins is enhanced in phenolic solvents. Scheme 6.28 gives some examples of the cycloadditions of 2,5-bis-(methoxycarbonyl)-3,4-diphenylcyclopentadienone **45** with styrene and cyclohexene in *p*-chlorophenol (PCP). Notice the result of the cycloaddition of cyclohexene which is known to be a very unreactive dienophile: in PCP at 80 °C the reaction works, while no Diels–Alder adduct was obtained in benzene. PCP also favors the decarbonylation of the adduct, generating a new conjugated dienic system, and therefore a subsequent Diels–Alder reaction is possible. Thus, the thermolysis at 170 °C for 10 h of Diels–Alder adduct **47**, which comes from the cycloaddition of **45** with 1,5-octadiene **46** (Scheme 6.29), gives the multiple Diels–Alder adduct **49** via decarbonylated adduct **48**. In PCP, the reaction occurs at a temperature about 50 °C lower than when performed without solvent, and product **49** is obtained by a one-pot procedure in good yield.



45

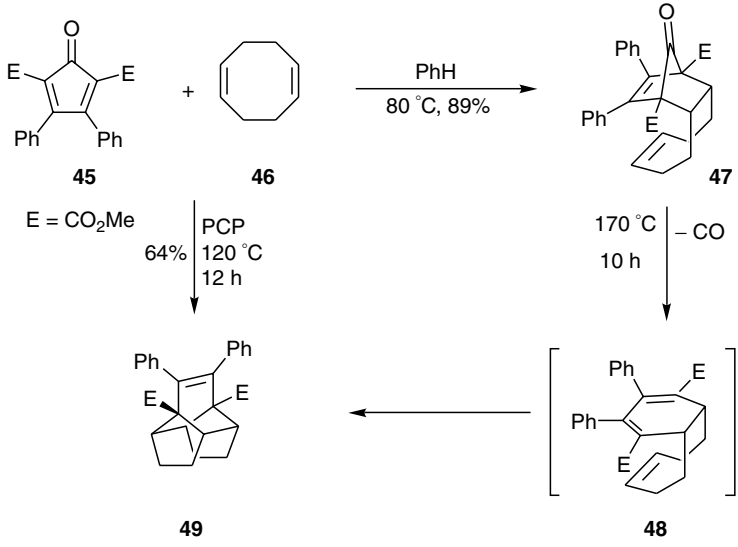
Medium	*T*(°C)	*t*(h)	*endo*/*exo*	k_{rel}	Yield(%)
PhH	r. t.	6	92:8	1	96
PCP	r. t.	1	80:20	4.5	91



45

medium	*T*(°C)	*t*(h)	*endo*/*exo*	k_{rel}	yield(%)
PhH	80	48	—	1	very low
PCP	80	72	50:50	8	88

Scheme 6.28

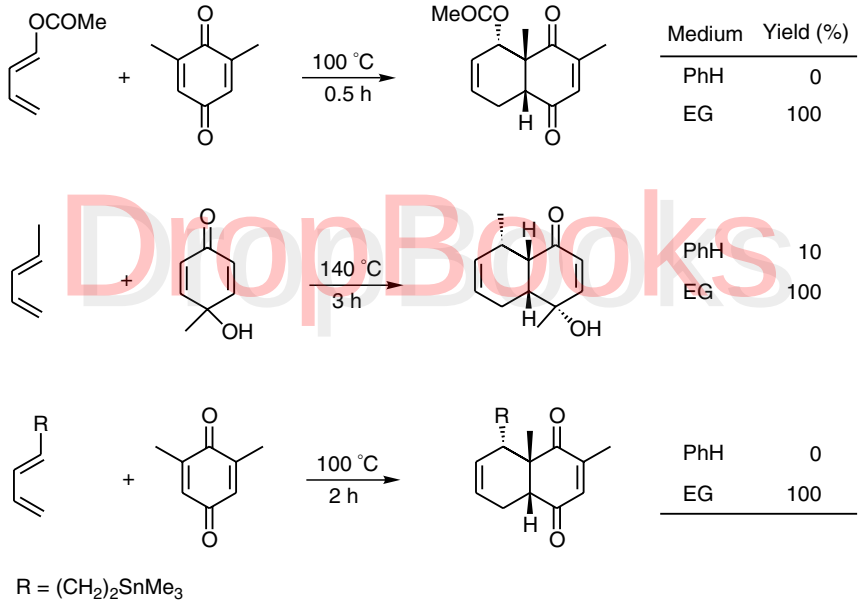


Scheme 6.29

Spectroscopic measurements indicate that PCP forms hydrogen bonds with carbonyl oxygen atoms of cyclopentadienone in both the ground and transition states, but the transition state is more effectively stabilized than the ground state, so a rate enhancement is observed.

The rates of intermolecular Diels–Alder reactions of hydrophobic dienes and dienophiles are significantly increased when the cycloadditions are performed in pure ethylene glycol (EG) [49a]. Some examples are illustrated in Scheme 6.30. This performance is due to the fact that the EG (i) forms extensive hydrogen bonding, (ii) is able to solubilize hydrophobic dienes and dienophiles, and (iii) forms molecular aggregations with the reactants.

Protic solvents such as *i*-PrOH and *t*-BuOH favor the diastereoselectivity of the reaction of 3-hydroxy-2-pyrone with acrylates [49b]. Further examples of proton-promoted Diels–Alder reactions are reported in Section 4.8.



DropBooks

Scheme 6.30

6.2.5 Ionic Liquids

Ionic compounds are generally crystalline solids which have high melting points because of the high energy of interaction between positive and negative ions (the lattice energy). Some big ions interact weakly and the lattice energy is so

low that the ionic compounds are liquid at room temperature. These liquids are made up entirely of ions and are known as ionic liquids.

According to the complexing ability of their anions, ionic liquids are classified as basic, neutral and acidic [50]. Some examples of neutral ionic liquids are reported in Table 6.9.

Room temperature ionic liquids are air stable, non-flammable, non-explosive, immiscible with many Diels–Alder components and adducts, do not evaporate easily and act as support for the catalyst. They are useful solvents, especially for moisture and oxygen-sensitive reactants and products. In addition they are easy to handle, can be used in a large thermal range (typically $-40\,^{\circ}C$ to $200\,^{\circ}C$) and can be recovered and reused. This last point is particularly important when ionic liquids are used for catalytic reactions. The reactions are carried out under biphasic conditions and the products can be isolated by decanting the organic layer.

Room temperature ionic liquids have been found to be excellent solvents for a number of reactions [50b] such as the isomerization [51], hydrogenation [52] and Friedel–Crafts reactions [53]. A number of Diels–Alder reactions were recently investigated in these systems.

Earle and coworkers [54] have performed Diels–Alder reactions in neutral ionic liquids. The results of reactions of cyclopentadiene with dimethyl maleate, ethyl acrylate and acrylonitrile are reported in Table 6.10. The cycloadditions proceeded at room temperature in all of the ionic liquids tested, except [BMIM]PF_4, and gave almost quantitative yields after 18–24 h. The *endo/exo* selectivity depends on dienophile. No enantioselectivity was observed in the [BMIM] lactate reaction.

The use of Lewis acids (ZnI_2, $BF_3 \cdot Et_2O$) in ionic liquids, tested in the cycloaddition of but-3-en-2-one with isoprene, increases both the rate and selectivity of the reaction. The ionic liquid remains catalytically active after the work-up and can be reused.

Table 6.9 Typical neutral ionic liquids

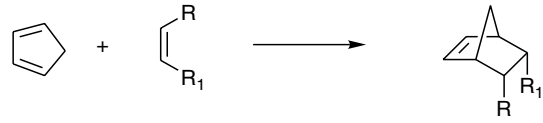
[BMIM]X	X = OTf, PF_6, BF_4, ClO_4, lactate
[ENIM]X	X = NO_3, PF_6
[ENIM]Cl · $AlCl_3$	organochloroaluminates
[BP] Cl · $AlCl_3$	organochloroaluminates

[BMIM] = 1-butyl-3-methylimidazolium cation

[EMIM] = 1-ethyl-3-methylimidazolium cation

[BP] = N-1-butylpyridinium cation

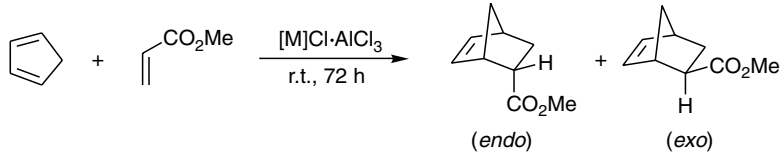
Table 6.10 Diels–Alder reactions of cyclopentadiene with dimethyl maleate, ethylacrylate and acrylonitrile in neutral ionic liquids



Ionic liquid	R	R_1	T (°C)	t(h)	*endo/exo*	Yield (%)
[BMIM]OTf	CO_2Me	CO_2Me	20	18	81:19	98
[BMIM]OTf	CO_2Et	H	20	18	86:4	96
[BMIM]OTf	CN	H	20	24	61:39	98
[BMIM]BF_4	CO_2Et	H	−15	24	83:17	99
[BMIM]PF_6	CO_2Et	H	20	1	89:11	36
[BMIM]lactate	CO_2Et	H	20	24	78:22	99

Similar results were obtained [55] for the Diels–Alder reaction between cyclopentadiene and methyl acrylate carried out in [EMIM]BF_4 at 20 °C for 72 h. In [EMIM]X (X = OTf, NO_3, PF_6) the reaction yields were lower [55]. The best yields and the highest *endo/exo* selectivity were obtained in [$EtNH_3$]NO_3 [56].

Chloroaluminate ionic liquids (typically a mixture of a quaternary ammonium salt with aluminum chloride: see Table 6.9) exhibit at room temperature variable Lewis acidity and have been successfully used as solvent/catalyst for Diels–Alder reactions [57]. The composition of chloroaluminate ionic liquids can vary from basic ([EMIM]Cl or [BP]Cl in excess) to acidic ($AlCl_3$ in excess) and this fact can be used to affect the reactivity and selectivity of the reaction. The reaction of cyclopentadiene with methyl acrylate is an example (Scheme 6.31).



(*endo*) (*exo*)

[M]Cl·$AlCl_3$ (% $AlCl_3$)	*endo/exo*	k_{rel}	Yield (%)
48 (basic)	84:16	1	95
51 (acidic)	95:5	24	79.4

M = EMIM, BP.

Scheme 6.31

The modest *endo/exo* ratio observed when the reaction was carried out in basic chloroaluminate ionic liquids is ascribable to the polarity of the medium, while the high diastereoselectivity found in the acidic mixture is due to the increase of Lewis/Bronsted acidity of the medium. The rates of the reactions performed in basic and acidic chloroaluminates ([EMIM]Cl·$AlCl_3$, [BP]Cl·$AlCl_3$) are seven times slower and ten times faster, respectively, than those observed when the reactions were carried out in water [57].

6.3 DIELS–ALDER REACTION IN MICROEMULSION

Microemulsions have been known for a century but the chemical research in the field received a great impulse when the price of oil reached levels that made it profitable to recover it by microemulsions.

The term microemulsion was first introduced in 1958 and 15 years later the microemulsion was recognized as a special kind of colloidal dispersion [58].

Today microemulsions are used in catalysis, preparation of submicron particles, solar energy conversion, extraction of minerals and protein, detergency and lubrication [58]. Most studies in the field of basic research have dealt with the physical chemistry of the systems themselves and only recently have microemulsions been used as a reaction medium in organic synthesis. The reactions investigated to date include nucleophilic substitution and additions [59], oxidations [59–61], alkylation [62], synthesis of trialkylamines [63], coupling of aryl halides [64], nitration of phenols [65], photoamidation of fluoroolefins [66] and some Diels–Alder reactions.

A microemulsion (μE) is a thermodynamically stable, transparent (in the visible) droplet type dispersion of water (**W**) and oil (**O**: a saturated or unsaturated hydrocarbon) stabilized by a surfactant (**S**) and a cosurfactant (**CoS**: a short amphiphile compound such as an alcohol or an amine) [67]. Sometimes the oil is a water-insoluble organic compound which is also a reactant and the water may contain mineral acids or salts. Because of the small dispersion size, a large amount of surfactant is required to stabilize microemulsions. The droplets are very small (about 100–1000 Å [68]), about 100 times smaller than those of a typical emulsion. The existence of 'giant' microemulsions (dispersion size about 6000 Å) has been demonstrated [58].

On a microscopic scale, a microemulsion is a heterogeneous system and, depending on the relative amounts of the constituents, three main types of structures can be distinguished [69]: oil in water (**O/W**, direct micellar structure), water in oil (**W/O**, reverse micellar structure) and a bicontinuous structure (**B**) (Figure 6.1). By adding oil in water, **O/W** dispersion evolves smoothly to a **W/O** dispersion via bicontinuous phases.

Microemulsions are excellent solvents for both non-polar organic molecules and inorganic reagents; they allow high local concentration of reactants and a

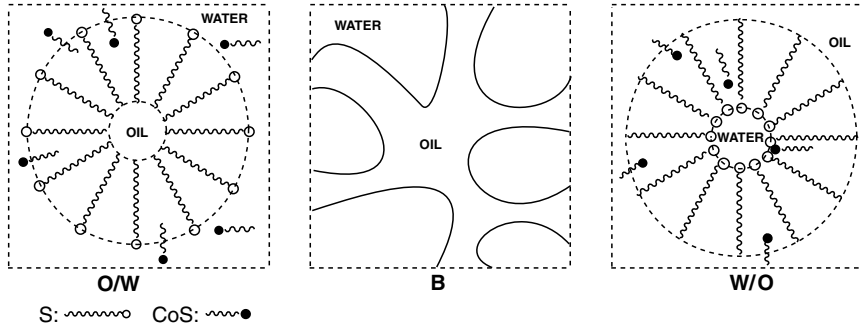


Figure 6.1

large internal interface and permit the reactants to assume preferential orientations. Therefore, a fast reaction rate and high selectivity are expected. Reactions usually take place at the oil–water interface in the micellar phase, but examples of reactions that occur in the bicontinuous phase are also known [70].

Non-aqueous microemulsions have been prepared by replacing water with formamide, a highly structured polar solvent [71]. Formamide enhances the solubility of organic compounds and is also used as a reactant.

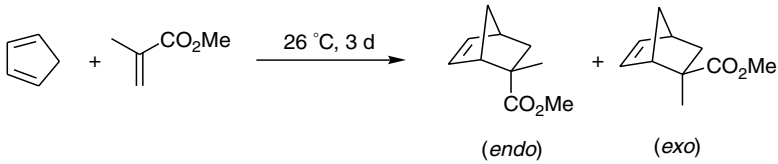
Physical–chemical studies require traces of additives (reactants, catalysts, electrolytes) with respect to the concentration of the basic components of the microemulsion, and this causes only a minor change in the phase behavior of the system. However, when the amounts of additives are on the scale used in organic synthesis, the phase behavior, which is very sensitive to the concentration of the reactants, is sometimes difficult to control and the reaction is carried out in a one-, two- or three-phase state.

DropBooks

The Diels–Alder reaction of methyl methacrylate with cyclopentadiene was studied [72] with solutions from three different regions of the pseudophase diagram for toluene, water and 2-propanol, in the absence and in the presence of surfactant [sodium dodecyl sulfate (SDS) and hexadecyltrimethylammonium bromide (HTAB)]. The composition of the three solutions (Table 6.11) corresponds to a **W**/**O**-μE (**A**), a solution of small aggregates (**B**) and a normal ternary solution (**C**). The diastereoselectivity was practically constant in the absence and in the presence of surfactant; a slight increase of *endo* adduct was observed in the **C** medium in the presence of surfactant. This suggests that the reaction probably occurs in the interphase and that the transition state has a similar environment in all three media.

The diastereoselection of the Diels–Alder reaction of methyl acrylate with cyclopentadiene was investigated [74] in microemulsions prepared with isooctane oil, CTAB as surfactant and 1-butanol as cosurfactant, and the results were compared with those found in pure solvents and water (Table 6.12). In emulsions rich in 1-butanol and formamide (entries 1 and 4) the reaction was slow (72 h) and the diastereoselectivity was practically the same as that

Table 6.11 Diastereoselectivity of Diels–Alder reaction of methyl methacrylate with cyclopentadiene performed in ternary solutions

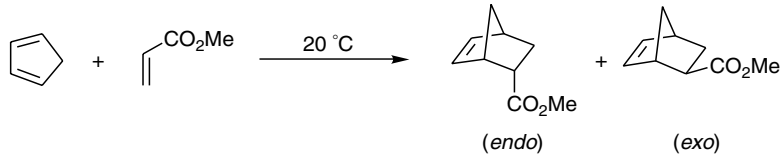


	Composition (mL %)			*exo* (%)		
Medium	H_2O	2-PrOH	PhH	None[a]	HTAB	SDS
A	4.9	44.6	50.5	63.2	63.9	63.5
B	4.9	56.9	38.2	63.4	60.9	60.5
C	5.2	71.5	23.3	63.5	54.2	53.5

[a] No added surfactant.

observed in pure solvents (entries 6 and 7). In the microemulsion μE-3 (reverse micelles), the reaction took place in the continuous phase and the *endo/exo* ratio was close to that found in pure isooctane. In the formamide-rich microemulsion μE-4 (direct micelles), the diastereoselections were virtually the same as those observed in 1-butanol-rich emulsion μE-1. It would seem that the reaction takes place at the micelle interface in the continuous formamide phase.

Table 6.12 Diastereoselectivity of Diels–Alder reaction of methyl acrylate with cyclopentadiene in formamide microemulsion and pure solvents



		Composition (weight %)				
Entry	Medium	C_8H_{18}[a]	$HCONH_2$[b]	1-BuOH[c]	CTAB[d]	*Endo* (%)
1	μE-1	1	6	90	3	82
2	μE-2	92	0.2	7.7	0.1	74
3	μE-3	72	4	22	2	79
4	μE-4	3	46	28	23	82
5	C_8H_{18}	100				70
6	$HCONH_2$		100			83
7	1-BuOH			100		83
8	H_2O[e]					90[73]

[a] Isooctane, [b] Formamide, [c] 1-Butanol, [d] Cetyltrimethylammoniumbromide, [e] only water.

6.4 DIELS–ALDER REACTION IN SUPERCRITICAL FLUIDS

A fluid is described as supercritical or subcritical if its temperature is above or below its critical temperature. Above the critical temperature the liquid and vapor phases are indistinguishable, the densities of the two phases become identical and the substance is described as a fluid, the physical properties of which are intermediate between those of a liquid and a gas [75].

Supercritical fluids (SCFs) have densities similar to those of liquids and a solvent power higher than that of gases, so that compounds which are insoluble in a fluid in ambient conditions become soluble in fluids under supercritical conditions [75].

Critical data for some substances, which are frequently used as solvents under supercritical conditions in chemical reactions, are reported [76] in Table 6.13.

Table 6.13 Critical temperature (T_c), pressure (P_c), density (D_c) and molar volume (V_c) for selected substances

substance	T_c(°C)	P_c (bar)	D_c(g/cm^3)	V_c(cm^3/mol)
Carbon dioxide	30.9	73.7	0.47	94
Ethane	32.2	48.8	0.20	145.5
Ethanol	240.7	61.4	0.28	168
Ethylene	9.1	50.4	0.21	131
Propane	96.6	42.5	0.22	200
Water	373.9	220.6	0.32	56

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Although SCFs have been known for a long time, they have received attention in organic chemical research and industrial application only during the last two decades [76a, 77].

Today SCFs are used for natural product extractions, chromatographic separations, pollution prevention, material processing and as solvents for chemical reactions.[75–77] Chemical applications include catalysis, polymerization, enzymatic reactions and organic synthesis.

The use of SCFs as solvents influences the reacting system because it is possible to dramatically change the density of the fluid with small perturbations of temperature and pressure and, in such a way, greatly affect the density-dependent bulk properties such as the dielectric constant, solubility and diffusibility of these compressible fluids.

Carbon dioxide and water are the most commonly used SCFs because they are cheap, nontoxic, nonflammable and environmentally benign. Carbon dioxide has a more accessible critical point (Table 6.13) than water and therefore requires less complex technical apparatus. Water is also a suitable solvent at temperatures below its critical temperature (superheated water). Other fluids used frequently under supercritical conditions are propane, ethane and ethylene.

A number of Diels–Alder reactions have been investigated in supercritical media and some of them will be illustrated. Most of the research has been focused on the influence of the pressure, which greatly influences the density of the fluid, on the kinetic aspects and on the product distribution of the reaction.

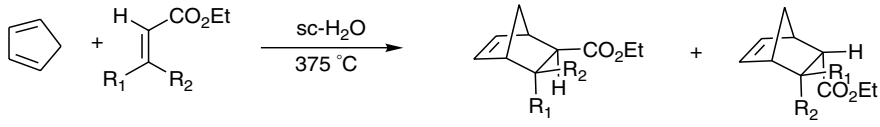
6.4.1 Diels–Alder Reaction in Supercritical Water (sc-H_2O)

Water in its supercritical state has fascinating properties as a reaction medium and behaves very differently from water under standard conditions [77f]. The density of sc-H_2O as well as its viscosity, dielectric constant and the solubility of various materials can be changed continuously between gas-like and liquid-like values by varying the pressure over a range of a few bars. At ordinary temperatures this is not possible. For instance, the dielectric constant of water at the critical temperature has a value similar to that of toluene. Under these conditions, apolar compounds such as alkanes may be completely miscible with sc-H_2O which behaves almost like a non-aqueous fluid.

Water reaches supercritical conditions at 373.9 °C (Table 6.13) but it becomes a suitable solvent at 200–350 °C and at pressures generated solely by the expansion of the liquid medium, about 20–100 bar (subcritical or superheated water).

Among the reactions studied in supercritical and subcritical water [77f, 78] the first report on a Diels–Alder reaction appeared in 1997 [79].

The results of Diels–Alder reactions of cyclopentadiene with diethyl fumarate, diethyl maleate and ethyl acrylate carried out in sc-H_2O are reported in Scheme 6.32 [79]. The cycloaddition of diethyl fumarate occurred with low yield,



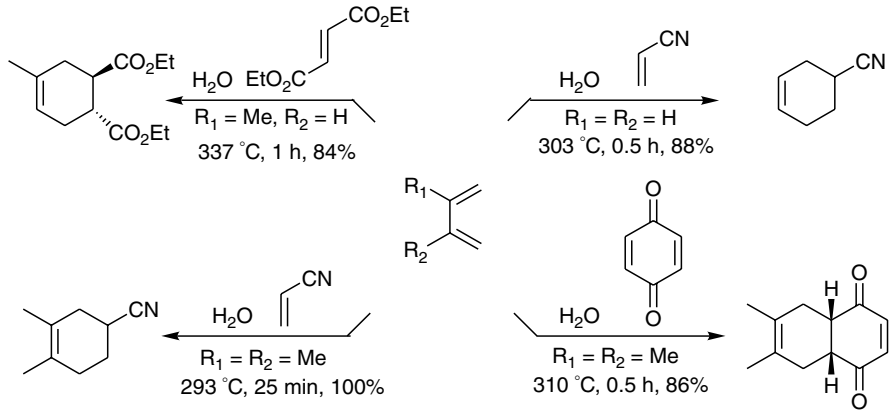
R_1	R_2	t (h)	*endo*/*exo*	Yield (%)
CO_2Et	H	1	–	10
H	CO_2Et	1	50:50	86
H	H	2	50:50	80

Scheme 6.32

while the other two dienophiles gave better results. The stereoselectivity of cycloaddition of ethyl acrylate depended on the reaction temperature and reaction time because the reaction undergoes reversion upon heating: at 375 °C after 2 h 50 % *endo*-adduct was observed, increasing to 75 % after 6 h.

Some other Diels–Alder reactions have been investigated in subcritical water [79] and some of them are illustrated in Scheme 6.33. The cycloadditions are fast and occur with good yields. In the absence of solvent, the reagents tend

to polymerize upon heating and no reaction occurs in water at temperatures below 280 °C.



Scheme 6.33

6.4.2 Diels–Alder Reaction in Supercritical Carbon Dioxide (sc-CO_2)

Above 30.9 °C, CO_2 cannot be liquefied by compression; it exists in a supercritical fluid phase (sc-CO_2) that behaves like a gas that is denser than liquid CO_2. Below 30.9 °C, CO_2 can be maintained as a liquid under relatively modest pressure; generally sc-CO_2 has better solvent properties than CO_2 in the subcritical liquid phase.

With sc-CO_2 high solubilities can be attained by increasing the pressure, and reactions can be carried out over a wide range of temperatures, pressures and densities. sc-CO_2 is readily available, nontoxic, nonflammable, chemically inert under many conditions, inexpensive, environmentally acceptable and easy to remove and recycle. It has received considerable attention as a reaction medium for organic synthesis [77d, 80] as well as in some large-scale extraction processes in food chemistry [81]. The Diels–Alder reaction in sc-CO_2 has been investigated quite thoroughly.

The diastereoselectivity of the cycloaddition of cyclopentadiene with methyl acrylate in sc-CO_2 at 40 °C and subcritical liquid CO_2 at 22 °C is practically the same (*endo*/*exo* = 75:25 and 76:24 respectively) and is comparable to that found in hydrocarbon solvents (73:27 and 75:25 in heptane and cyclohexane, respectively). This shows that CO_2, in these states, behaves like an apolar solvent with very low polarizability [82].

The effect of pressure on the rate constant of the Diels–Alder reaction between maleic anhydride and isoprene was investigated in sc-CO_2 at 35 °C and at pressures ranging from 90 to 193 bar. For comparison purposes, the reaction was also carried out in an apolar solvent such as propane under

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subcritical conditions (80 °C and 90–152 bar) [83]. In sc-CO_2, the mole fraction-based rate constants varied linearly with the density of the solution, while in subcritical propane the rate constants deviated from a linear dependence on density at the lower pressures studied.

The Diels–Alder reactions of maleic anhydride with 1,3-cyclohexadiene, as well the parallel reaction network in which maleic anhydride competes to react simultaneously with isoprene and 1,3-cyclohexadiene [84], were also investigated in subcritical propane under the above reaction conditions (80 °C and 90–152 bar). The reaction selectivities of the parallel Diels–Alder reaction network diverged from those of the independent reactions as the reaction pressure decreased. In contrast, the same selectivities were obtained in both parallel and independent reactions carried out in conventional solvents (hexane, ethyl acetate, chloroform) [84].

The rate of the Diels–Alder reaction between *p*-benzoquinone and cyclopentadiene was measured in sc-CO_2 and subcritical CO_2 [85]. Relative reaction rates at different pressures are reported in Table 6.14. On going from CO_2 in the liquid phase (below 31 °C) to sc-CO_2, the reactivity increased significantly only when the reaction was carried out under high pressure. At 30 °C and 60 bar the reaction was 1.36 times faster than when it was performed in diethyl ether at 30 °C and 1 bar.

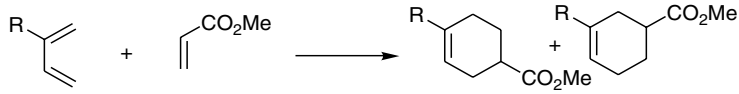
An example of a *hetero*-Diels–Alder reaction in sc-CO_2 is the cycloaddition of anthracene with 4-phenyl-1,2,4-triazoline-3,5-dione, carried out at 40 °C and at a pressures between 75 and 216 bar [86]. The rate constant increases with decreasing pressure and the highest reactivity was observed at the critical pressure. The value of the rate constant at the critical pressure was higher than that observed in liquid $CHCl_3$ and MeCN at the same temperature. At higher pressures, the rate is slower than that in the polar solvents, which reflects the apolar nature of sc-CO_2 as a solvent.

A systematic study of the effect of pressure and density on the regiochemical course of the Diels–Alder reactions of methyl acrylate and 2-substituted 1,3-butadienes carried out in sc-CO_2 was recently reported [87]. The reactions were compared with those carried out in a conventional medium such as toluene. Some results are illustrated in Table 6.15.

Table 6.14 Relative rates of cycloadditions of *p*-benzoquinone and cyclopentadiene in carbon dioxide

T(°C)	P(bar)	$k_{rel}(k_T/k_{25}°C)$
25	60	1
30	60	1.32
35	120	1.40
35	180	1.66
40	120	1.74
40	180	1.85
40	240	1.92

Table 6.15 Regioselectivity of Diels–Alder reactions of methyl acrylate with 2-substituted-1,3-butadienes in sc- CO_2 and PhMe



	sc-CO_2[a]				PhMe[b]		
R	T(°C)	P (bar)	t (d)	*para*/*meta*	T(°C)	t (d)	*para*/*meta*
Me	50	49.5	4	73:27	50	3	69:31
	50	117	3	70:30	145	0.01	71:29
t-Bu	50	87	3	71:29	50	3	69:31
	50	117	1	65:35			
$OSiMe_3$	50	90		traces	110	0.03	87:13
	50	117	1	85:15			

[a] Yield 3–54%,
[b] Yield 48–78%.

The regioselectivity under supercritical conditions at different pressures varied little from that found in toluene solution; in particular, no reversal in regioselectivity was found in sc-CO_2 near the critical pressure [88].

The combination of Lewis-acid catalysis and sc-CO_2 has also been investigated. One of these studies involved the $AlCl_3$-catalyzed Diels–Alder reaction of isoprene and maleic anhydride in sc-CO_2 at 67 °C and at 74.5–78.5 bar [89]. The reaction rate was enhanced with respect to the uncatalyzed reaction and an unconcerted two-step mechanism was suggested [89].

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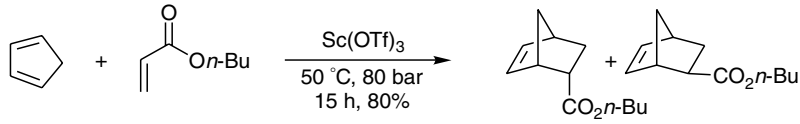
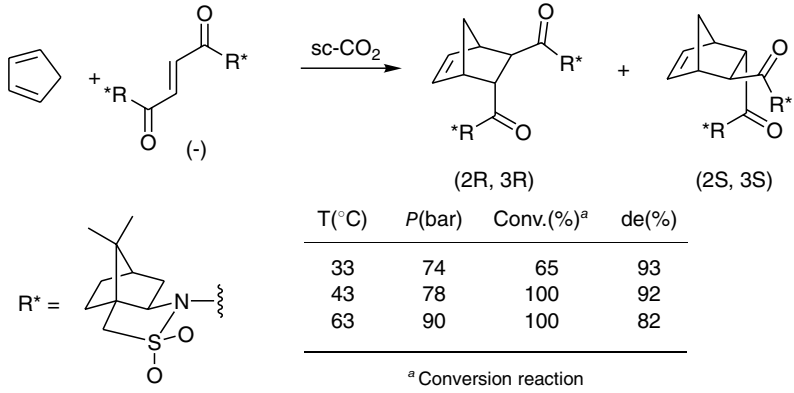
A recent report [90] investigated the Diels–Alder reaction of cyclopentadiene with various acrylates in sc-CO_2 catalyzed by $Sc(OTf)_3$. The results relative to *n*-butyl acrylate, in sc-CO_2 and in conventional solvents, are reported in Scheme 6.34. The catalyzed reaction carried out under supercritical conditions went to completion within 15 h at 50 °C, whereas the uncatalyzed reaction proceeded only to 10 % after 24 h. An increase of *endo/exo* diastereoselectivity was also observed.



Medium	P (bar)	*endo*/*exo*
PhMe	1	91:9
$CHCl_3$	1	92:8
sc-CO_2	80	96:4

Scheme 6.34

Chapuis, Jurczak and coworkers [91] were the first to report the influence of sc-CO_2 on the enantioselectivity of a Diels–Alder reaction (Scheme 6.35). At subcritical conditions the conversion of the reaction was poor. The best enantioselectivity was achieved around the critical point and no improvement was observed at higher pressure and temperature.



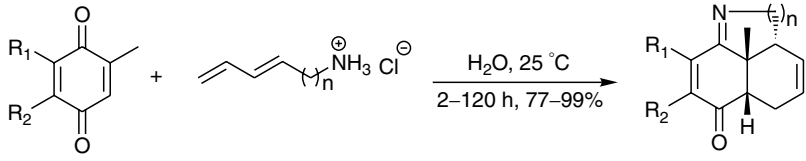
T(°C)	P(bar)	Conv.(%)[a]	de(%)
33	74	65	93
43	78	100	92
63	90	100	82

[a] Conversion reaction

Scheme 6.35

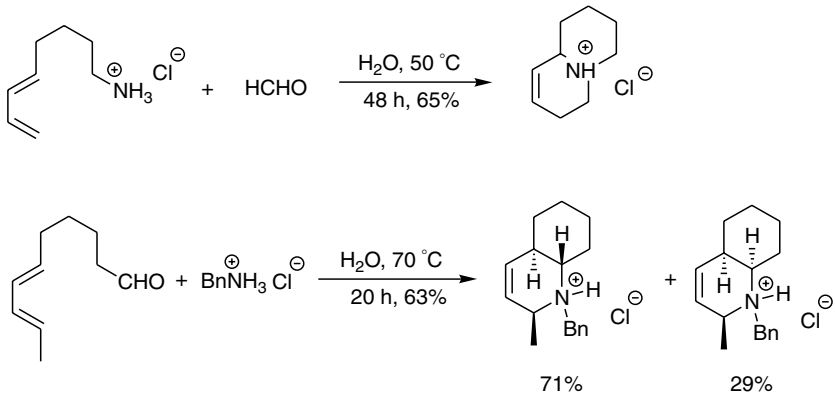
6.5 OUTLINED DIELS–ALDER REACTIONS

Reaction of (E)-2,4-pentadienyl ammonium chloride and related ammonium salts with dienophiles in water [92]

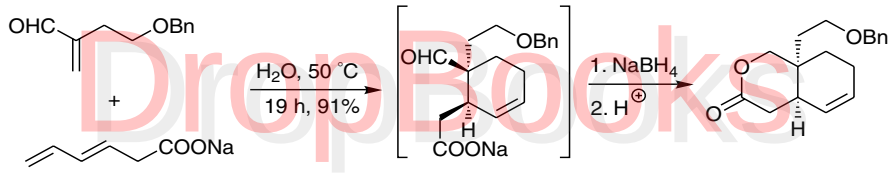


R_1 = Me, OMe R_2 = H, Me; n = 1, 2

Aza-Diels–Alder reactions in aqueous solutions: cycloaddition of dienes with simple iminium salts generated under Mannich conditions [22]

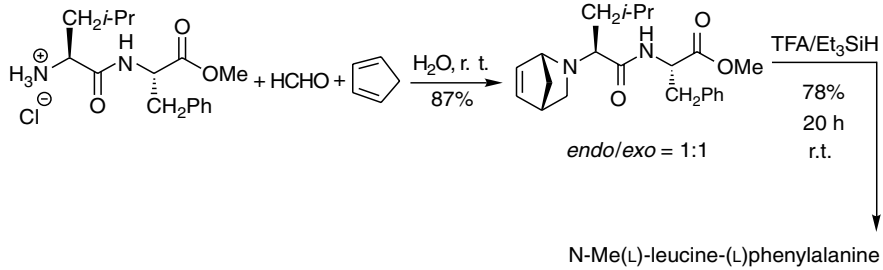


Aqueous intermolecular Diels–Alder chemistry: vernolepin revisited [16e]

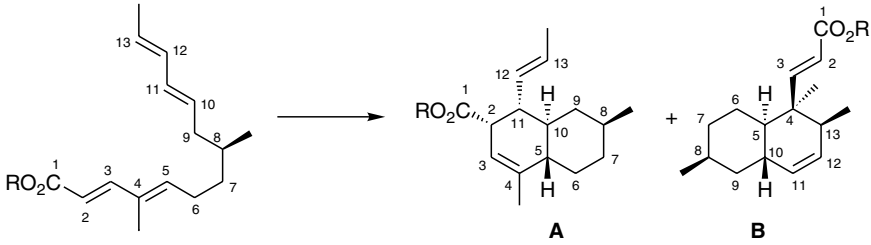


DropBooks

Immonium ion based synthetic methodology: a novel method for the N-methylation of dipeptides and amino acid derivatives via retro aza-Diels–Alder reactions [93]

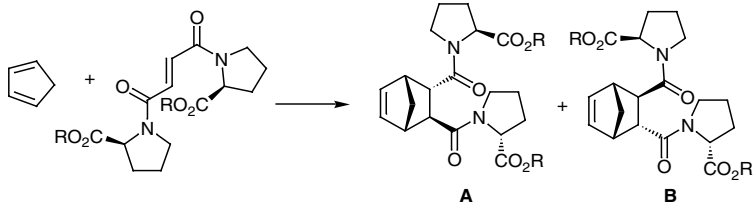


Intramolecular Diels–Alder cycloadditions of bis-diene substrates [94]



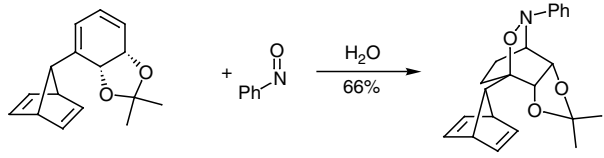
R = H	H_2O	100 °C	A = 11%	B = 89%
R = Et	H_2O	100 °C	A = 40%	B = 60%
R = Et	PhMe	165 °C	A = 75%	B = 25%

Double asymmetric synthesis and a new strategy for stereochemical control in organic synthesis [95]



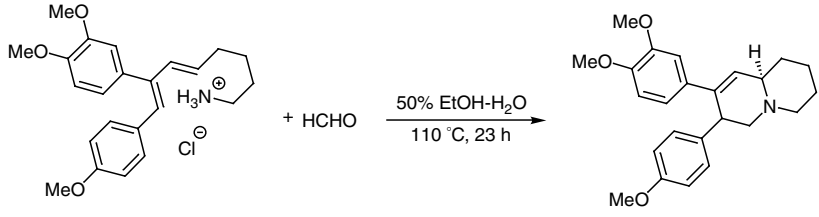
R = Bn	H_2O/EtOH	-10 °C	**A**/**B** = 96:4	Yield 100%
R = Bn	PhMe	0 °C	**A**/**B** = 93.5:6.5	Yield 100%

The oxidation of norbornadiene and some derivatives using *Pseudomonas* sp [96].

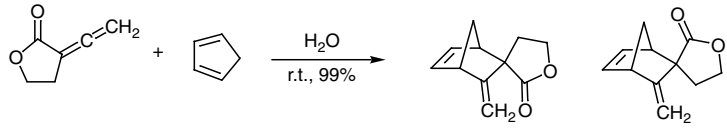


three dienophiles

Quinolizidine synthesis via intramolecular immonium ion based Diels–Alder reactions: total synthesis of (±)-lupinine, (±)-epilupinine, (±)-criptopleurine and (±)-julandine [97]



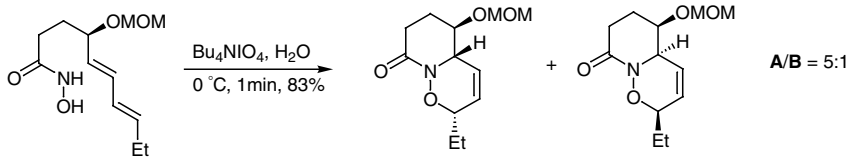
High exoselectivity in Diels–Alder addition of α-vinylidene and α-methylene-γ-butyrolactones to cyclopentadiene [98]



(*endo*) (*exo*)

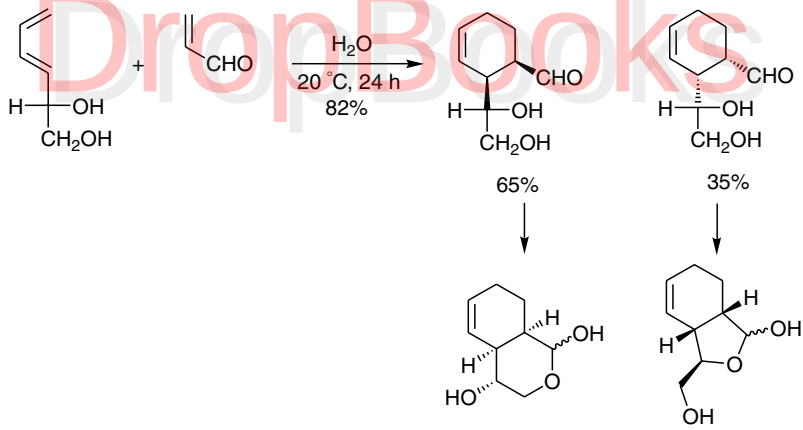
exo/*endo* = 79:21

Enhanced stereoselectivity in aqueous intramolecular hetero-Diels–Alder cycloaddition of chiral acylnitroso compounds [17c, d, 99]



7 examples **A** **B**

Aqueous cycloaddition using glyco-organic substrates. Facial stereoselectivity in Diels–Alder reactions of a chiral diene derived from D-glyceraldehyde [102]



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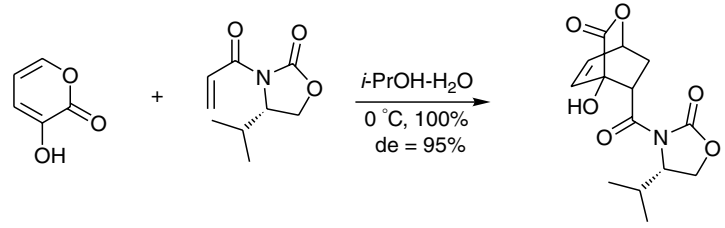
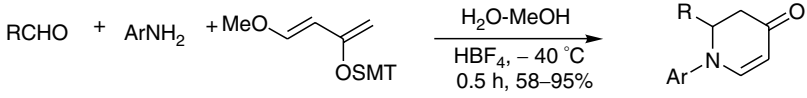
Asymmetric base-catalyzed Diels–Alder reaction of 3-hydroxy-2-pyrone with chiral acrylate derivatives [106]

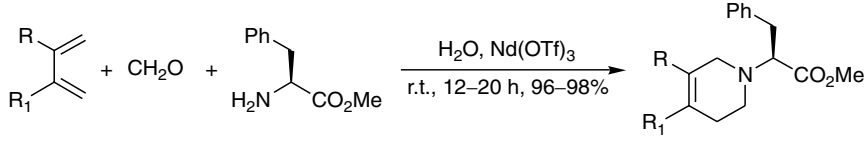


Bronsted acid catalyzed aza-Diels–Alder reaction of Danishefsky's diene with aldimine generated *in situ* from aldehyde and amine in aqueous media [107]

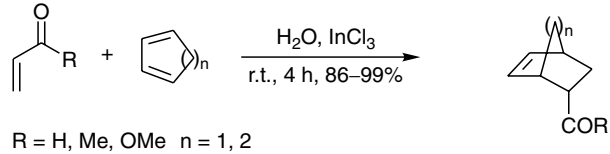


R = Ph, p-MeC_6H_4, *p*-$NO_2C_6H_4$, *c*-C_6H_{11}, $BnCH_2$, *i*-Pr, 2-Furyl Ar, = Ph, p-$MeOC_6H_4$

Lanthanide triflates as unique Lewis acids [24d]



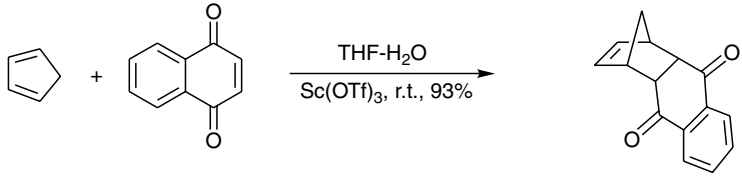
Indium trichloride ($InCl_3$) catalyzed Diels–Alder reaction in water [30]



R = H, Me, OMe n = 1, 2

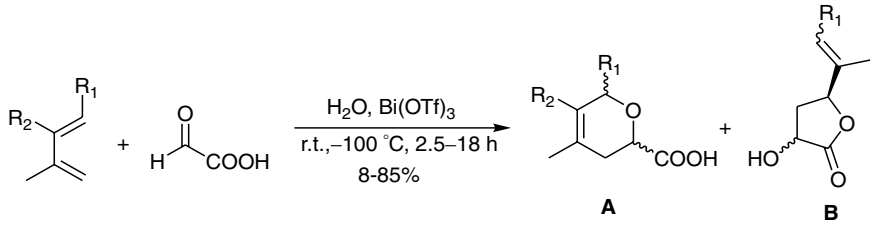
13 examples

Scandium trifluoromethansulfonate ($Sc(OTf)_3$). A novel reusable catalyst in the Diels–Alder reaction [108]



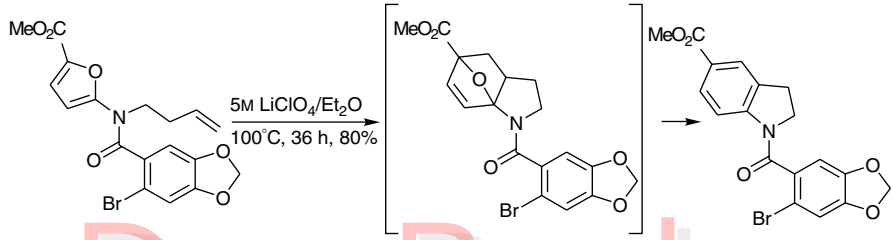
100%

Enhancement of dienophilic and enophilic reactivity of the glyoxylic acid by bismuth (III) triflate in the presence of water [28]



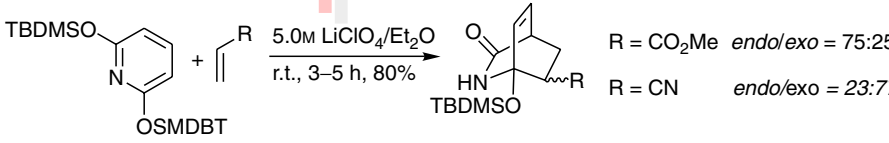
R_1, R_2 = H, Me **A/B** = 43–99%: 57–1% **A** (*cis/trans*) = 40–64%:60–36%

IMIDAF cycloaddition as a method for the preparation of pyrrolophenanthridine alkaloids [44]



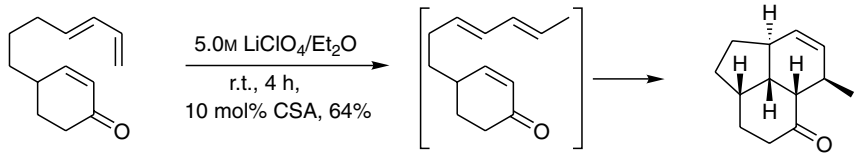
DropBooks

Dramatic rate accelerations of Diels–Alder reactions in 5M lithium perchlorate–diethyl ether: the cantaridin problem reexamined [34]



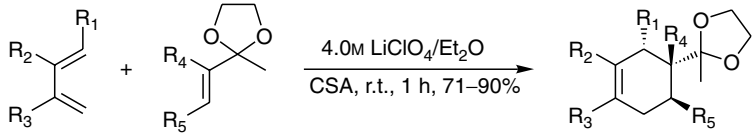
8 examples

Acid catalyzed intramolecular Diels–Alder reactions in lithium perchlorate–diethyl ether: acid promoted migration of terminal dienes prior to [4 + 2] cycloaddition in conformationally restricted substrates [101]



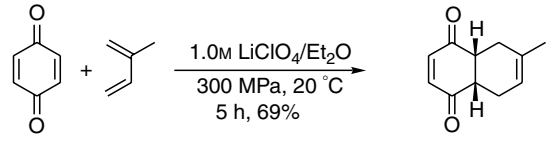
3 examples

Acid catalyzed ionic Diels–Alder reactions in concentrated solutions of lithium perchlorate in diethyl ether [43]



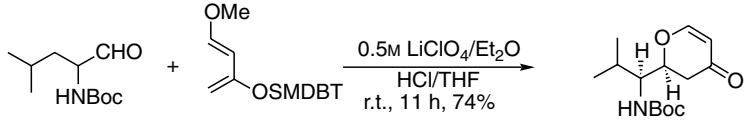
R_1-R_5 = H, Me

The cause of the rate acceleration by diethyl ether solutions of lithium perchlorate in organic reactions. Application to high pressure synthesis [35c]



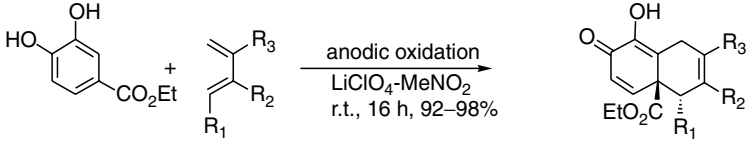
5 examples

Lithium catalyzed hetero-Diels–Alder reactions. Cyclocondensation of N-protected α-amino aldehydes with 1-methoxy-3-*tert*-butyldimethylsilyloxybutadiene in the presence of lithium perchlorate [104]



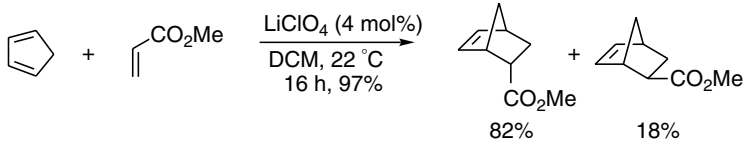
7 examples

Diels–Alder reactions of quinones generated *in situ* by electrochemical oxidation in lithium perchlorate–nitromethane [105]

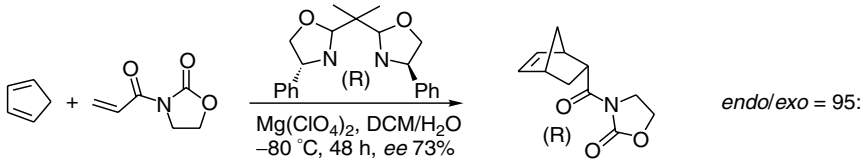


R_1, R_2, R_3 = H, Me 15 examples

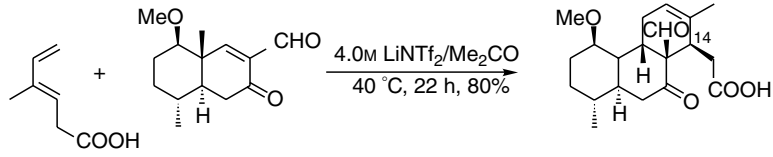
Catalysis by lithium perchlorate in dichloromethane: Diels–Alder reactions and 1,3-Claisen rearrangements [100]



Can a chiral catalyst containing the same ligand/metal components promote the formation of both enantiomers enantioselectively? The bis(oxazoline)magnesium perchlorate-catalyzed asymmetric Diels–Alder reaction [103]



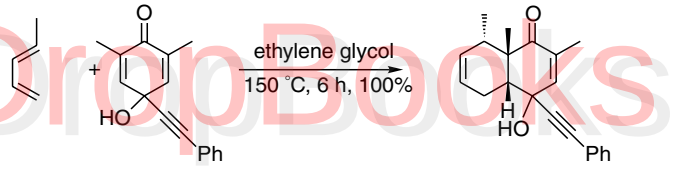
Lithium trifluoromethanesulfonimide in acetone or diethyl ether as a safe alternative to lithium perchlorate in diethyl ether for effecting Diels–Alder reactions. Unexpected influence of the counterion on *exo*/*endo* selectivity [47]



7 examples

C(14)β-H/C(14)α-H = 3.6

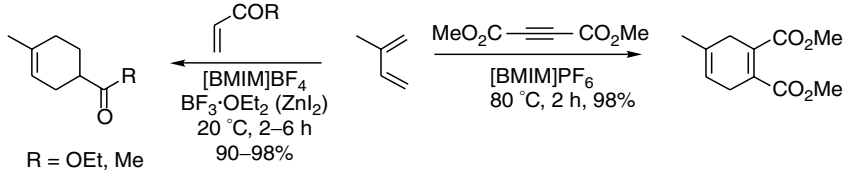
Molecular aggregation and its applicability to synthesis. The Diels–Alder reaction [49]



7 examples

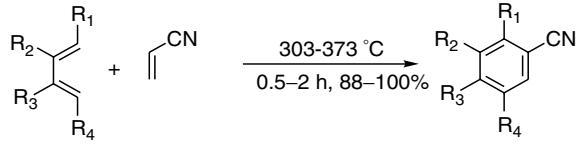
DropBooks

A safe recyclable alternative to lithium perchlorate–diethyl ether mixture [54]



R = OEt, Me

Diels–Alder reactions using supercritical water as an aqueous solvent medium [79]



R_1, R_4 = H, Ph R_2, R_3 = H, Me

12 examples

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Dropbooks

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7 Diels–Alder Reaction Compilation

The titles of books, reviews, monographs and symposia proceedings published in the years 1990–2000, together with some edited in the first months of 2001, that were entirely or partly devoted to Diels–Alder reactions, are reported below. Some key words illustrating the subject are included. Sources are given as a four-figure number, the first two figures indicating the year of publication and the second two the sequence; thus 0003 refers to source number 3 of the year 2000, and 9118 to source number 18 of 1991. The numbers are used for reference in a keyword index at the end of the chapter. Unless otherwise specified, the sources are written in English.

7.1 COMPILATION

2001

(0101) Fringuelli F., Piermatti O., Pizzo F., Vaccaro L. **Recent Advances in Lewis-Acid Catalyzed Diels–Alder Reactions in Aqueous Media** *Eur. J. Org. Chem.* **2001** 439–455
Keywords: water, Lewis acids, carbo-Diels–Alder reactions, *hetero*-Diels–Alder reactions

(0102) Kumar A. **Salt Effects on Diels–Alder Reaction Kinetics** *Chem. Rev.* **2001** *101* 1–19

2000

(0001) Warmuth R **The Inner Phase of Molecular Container Compounds As a Novel Reaction Environment** *J. Inclusion Phenom. Macrocyclic Chem.* **2000** *37* 1–38
Keywords: inclusion reaction, photochemistry, photoinduced electron transfer, fullerenes

(0002) Hamers R. J., Coulter S. K., Ellison M. D., Hovis J. S., Padowitz D. F., Schwartz M. P., Greenlief C. M., Russell J. N. Jr **Cycloaddition Chemistry of Organic Molecules With Semiconductor Surfaces** *Acc. Chem. Res.* **2000** *33* 617–624
Keywords: carbonyl group, semiconductor materials, surface reaction, alkenes, aromatic compounds, azo compounds, cycloalkadienes, isothiocyanates, unsaturated compounds

(0003) Tokoroyama T. **Synthesis of Clerodane Diterpenoids and Related Compounds – Stereoselective Construction of the Decalin Skeleton With Multiple Contiguous Stereogenic Centers** *Synthesis* **2000** 611–633
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